Pharmacodynamics and pharmacokinetics of budesonide: A new nebulized corticosteroid

Stanley J. Szefler, MD *Denver, Colo*

Underutilization of anti-inflammatory agents in the treatment of asthma has received widespread attention. Inhaled glucocorticosteroids are important agents for the management of asthma in children and adults. Budesonide has a high ratio of topical anti-inflammatory to systemic activity and is one of the most extensively used inhaled glucocorticoids. Budesonide inhalation suspension is the first formulation designed to deliver budesonide by way of nebulization for infants and children under 8 years of age with persistent asthma. Budesonide decreases airway hyperresponsiveness and reduces the number of inflammatory cells and mediators present in the airways of patients with asthma. Budesonide appears to be retained within cells, allowing for a once-daily treatment regimen in certain patient groups. After inhalation of nebulized budesonide, absorption is rapid. Data suggest that plasma concentrations of budesonide are similar in adults and children after inhalation of the same nominal dose from a nebulizer. In children 3 to 6 years of age, total systemic availability of budesonide after dosing with a jet nebulizer was approximately 6% of the labeled dose. Budesonide is highly protein bound, undergoes extensive first-pass hepatic metabolism, is metabolized by the liver cytochrome P450 system, and is primarily excreted in the urine as metabolites. In children 3 to 6 years of age, the volume of distribution at steady state of budesonide inhalation suspension is approximately 3 L/kg, with a terminal elimination half-life of 2.3 hours; systemic clearance is approximately 30 mL/kg. The pharmacodynamic and pharmacokinetic properties of budesonide inhalation suspension allow for potent local anti-inflammatory activity with limited systemic exposure. (J Allergy Clin Immunol 1999;104:S175-83)

Key words: *Budesonide, budesonide inhalation suspension, asthma, inhaled corticosteroid, pharmacokinetics, pharmacodynamics*

Inflammation is a critical feature in the pathogenesis of asthma,[1] and the underutilization of anti-inflammatory glucocorticoids in the treatment of asthma has recently received widespread attention.[2,3] Inhaled corticosteroids are now recommended for use in all but the mildest cases of persistent asthma.[3] However, for many patients under 4 years of age, it is difficult to use available delivery systems effectively, because this age group typically lacks the necessary coordination skills and understanding required for optimal drug delivery.[4]

Abbreviations used
AUC: Area under the plasma concentration-time curve
BIS: Budesonide inhalation suspension
LTD_4: Leukotriene D_4
pMDI: Pressurized metered-dose inhaler

Budesonide inhalation suspension (BIS; Pulmicort Respules™; AstraZeneca, Wayne, Pa) is the first formulation designed to deliver a corticosteroid by way of nebulization and will be the first inhaled corticosteroid for use in children younger than 4 years of age in the United States. Budesonide has been available for more than 15 years outside the United States as a nebulized suspension, as a pressurized metered-dose inhaler (pMDI) and as a dry powder inhaler (Pulmicort Turbuhaler®; AstraZeneca). Pulmicort Respules has been approved in more than 35 countries outside the United States, including Canada and the United Kingdom. Pulmicort Turbuhaler is now available in the United States for the treatment of patients with asthma who are 6 years of age and older. Budesonide also is approved in the United States for the treatment of allergic rhinitis. The human pharmacokinetics and pharmacodynamics of budesonide have been investigated thoroughly through the intravenous, oral, pulmonary, nasal inhalation, and rectal routes of administration and are reviewed elsewhere.[5,6] This report summarizes the pharmacodynamics and pharmacokinetics of budesonide and focuses on pharmacokinetics of BIS in the pediatric population.

PHARMACOLOGY AND PHARMACODYNAMICS OF BUDESONIDE

Budesonide ([RS]-1β, 16α 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with butyraldehyde) is a nonhalogenated corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity (Fig 1).[5,7] Corticosteroid actions are mediated by the glucocorticoid receptor, which is found in the cytoplasm of most cell types.[8,9] Corticosteroids like budesonide have a wide range of inhibitory activities against many cell types (eg, lymphocytes, eosinophils, mast cells, neutrophils, and macrophages) and mediators involved in allergic- and nonallergic-mediated inflammation (eg, cytokines, histamine, eicosanoids, and leukotrienes).[7,10]

From the Division of Clinical Pharmacology, National Jewish Medical and Research Center, and the Departments of Pediatrics and Pharmacology, University of Colorado Health Sciences Center.
Reprint requests: Stanley J. Szefler, MD, Department of Pediatrics, Room J209, National Jewish Medical and Research Center, 1400 Jackson St, Denver, CO 80206.

0091-6749/99 $8.00 + 0 **1/0/100811**

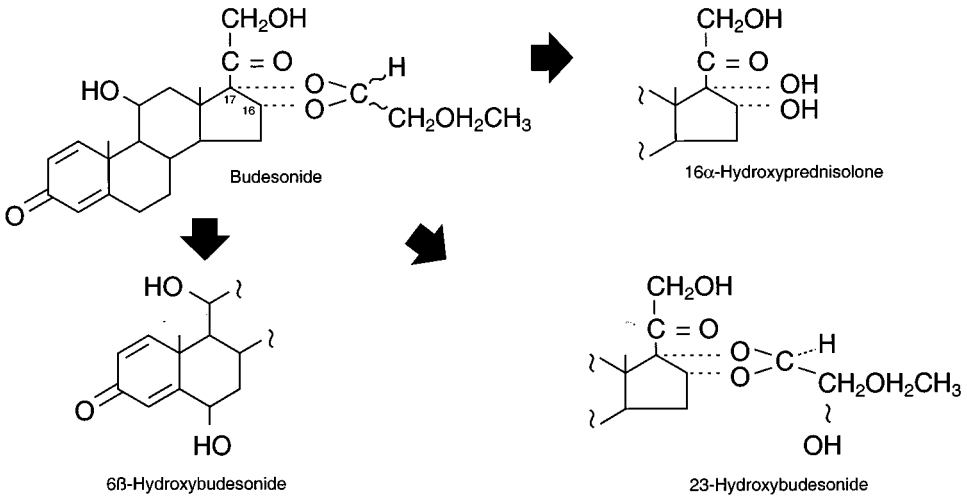

FIG 1. Chemical structure of budesonide and its metabolites.

In addition, corticosteroids increase the synthesis of anti-inflammatory proteins, such as lipocortin-1, secretory leukocyte protease inhibitor, and IL-10, and increase the expression of β_2-adrenergic receptors.[8] These anti-inflammatory actions may contribute to the efficacy of corticosteroids in asthma.[8,10,11]

Receptor affinity

Compared with previously developed inhaled steroids, budesonide has a high relative affinity for the glucocorticoid receptor.[12-14] In standard in vitro tests and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol.[7] Budesonide is a 1:1 racemic mixture of 2 epimers, 22R and 22S, that do not interconvert. Both epimers exhibit high glucocorticoid activity, with the 22R epimer having 2-fold greater affinity than the 22S epimer.[7]

Relative activity

In patients with asthma, potent topical anti-inflammatory action is necessary to relieve airway inflammation; however, this often is achieved at the expense of increased systemic exposure. Structure–activity studies demonstrate that the 16, 17-acetal side chain of budesonide (Fig 1) confers highly potent topical anti-inflammatory activity[15] with low systemic activity. Budesonide has demonstrated a high ratio of local anti-inflammatory activity to systemic activity in preclinical and clinical studies,[15-17] which is explained by a potent anti-inflammatory effect, extensive first-pass hepatic metabolism of orally absorbed drug (85%-95%),[16,17] and low potency of budesonide metabolites.[15]

In human skin blanching assays, budesonide has been shown to be more potent than many of the available glucocorticoids, including beclomethasone dipropionate, flunisolide, and triamcinolone acetonide (Fig 2).[16-20] Budesonide has an antiasthmatic potency approximately 58 times that of prednisone.[22]

In healthy volunteers, systemic activity of budesonide (measured as changes in cortisol and total and differential white cell counts) was 2 to 4 times less than that of beclomethasone dipropionate after oral intake.[16,19] After inhalation of these 2 agents, the differences in systemic activity were less pronounced, yet still significant, with a much weaker systemic effect observed with budesonide.[19,23]

The therapeutic effects of conventional doses of orally inhaled budesonide can be explained by its direct local action on the respiratory tract.[7] To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a randomized trial compared budesonide 400 μg administered by way of a pMDI (with a tube spacer) with oral budesonide 1400 μg and placebo in 47 patients with asthma.[24] The oral dose corresponds to approximately 50% greater systemic exposure than the inhaled dose; a larger oral dose was chosen to diminish the risk for a type II error (ie, failure to detect an antiasthmatic effect with oral budesonide). Patients were followed weekly until asthma relapsed (defined as a drop in the mean peak expiratory flow rate from baseline by more than 2 SEMs) or for 8 weeks if no relapse occurred. Time to relapse was significantly longer for inhaled budesonide than oral budesonide (22 vs 7.9 days, respectively; $P = .003$) or placebo (22 vs 9 days, respectively; $P = .004$) and did not differ between oral budesonide or placebo. This trial demonstrated the efficacy of inhaled budesonide and that systemically circulating budesonide lacks any measurable antiasthmatic effect.

Effects on inflammatory cells and mediators

Reduction in the number of inflammatory cells in bronchial mucosa correlates with clinical improvement in patients with asthma.[25] In vitro evidence suggests that budesonide may phenotypically alter alveolar macrophages,[26] reduce histamine release from basophils,[27,28] inhibit monocyte-mediated cytotoxicity[29] and eosinophil activation,[30] and induce the activity of neutral endopeptidase.[31]

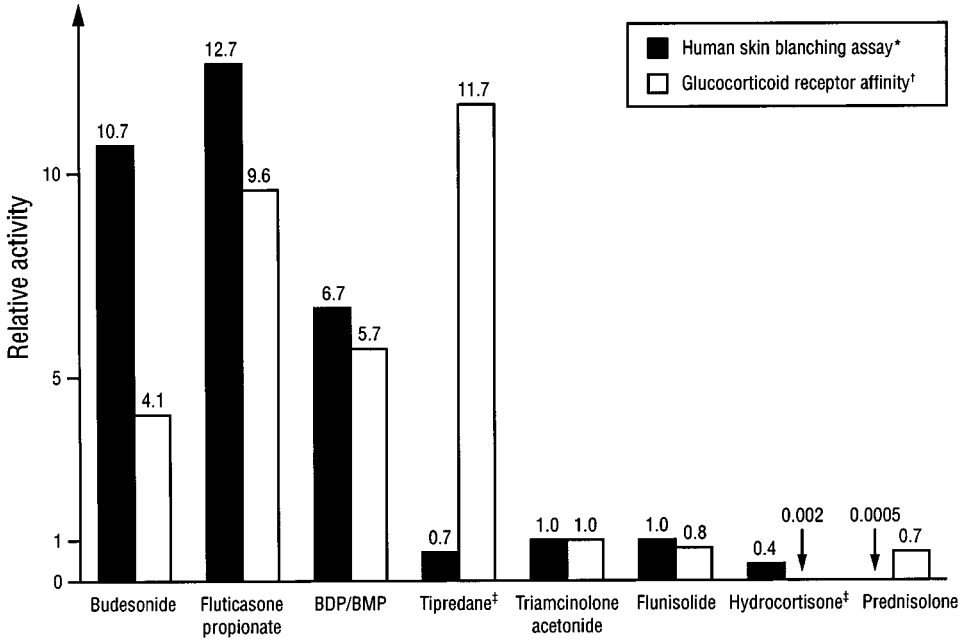

FIG 2. The relative activity of glucocorticoids by the human skin-blanching assay and glucocorticoid receptor affinity. *BDP*, beclomethasone dipropionate; *BMP*, beclomethasone monopropionate. *Skin blanching data compiled from references 16-20; †glucocorticoid receptor data compiled from references 16,17, and 21; ‡stripped skin version of the McKenzie vasoconstriction assay.

Numerous studies have evaluated the effects of inhaled budesonide on airway inflammation in patients with asthma by performing endobronchial biopsies before and after treatment.[32-35] In 1 trial involving 6 patients with asthma,[32] inhaled budesonide therapy (400 μg twice daily for 3 months) reduced both T-cell–mediated inflammation in the bronchial wall and bronchial hyperresponsiveness. In a randomized, double-blind, placebo-controlled trial in 16 patients with asthma,[33] inhaled budesonide (800 μg daily for 6 months) resulted in a significant reduction in the numbers of mast cells (P = .003), activated eosinophils (P = .017), and expression of human leukocyte antigen-DR (P = .034) compared with placebo. Another randomized, double-blind trial[35] compared budesonide 600 μg twice daily for 3 months with terbutaline 375 μg twice daily in 14 adult patients. Budesonide significantly (P < .01) reduced the number of inflammatory cells present in the airway epithelium (including lymphocytes, mast cells, eosinophils, neutrophils, and macrophages); the total number of cells did not decrease with terbutaline therapy. Thus reductions in the numbers of mast cells and activated eosinophils appear to contribute to the anti-inflammatory effects of budesonide.

Effects on airway hyperresponsiveness

Inhalation of glucocorticoids is associated with decreased airway hyperresponsiveness.[36] Budesonide administered with the Turbuhaler has been shown in various challenge models (including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate) to decrease airway reactivity in patients with hyperreactive airways.[7,37-39] In 1 randomized trial,[37] 103 newly diagnosed patients with asthma received either budesonide 600 μg twice daily or terbutaline 375 μg twice daily for 2 years. After 6 weeks of therapy, patients treated with budesonide tolerated inhaled histamine significantly better than patients treated with terbutaline (P < .001). In the budesonide group, the marked decrease in airway hyperresponsiveness was observed after 6 weeks of therapy; although this decrease continued, the trend over time was not significant. Similar results have been reported in adult patients with asthma who receive inhaled budesonide 800 μg twice daily for 6 weeks[40] and in patients who receive 400 μg to 800 μg daily for longer than 1 year.[38]

After inhaled allergen challenge, pretreatment with budesonide 800 μg twice daily administered with the Turbuhaler for 2 weeks reduced the acute (early phase) and delayed (late phase) pulmonary reaction, with a measured reduction in FEV_1.[7] Budesonide appears to attenuate both the early-phase and late-phase reactions to allergen challenge after a single dose and with short-term dosing.[41-43] In a randomized, double-blind trial[44] involving children with mild asthma, budesonide 200 μg 3 times daily or placebo was administered within 20 to 24 hours after exposure to house dust–mite antigen and histamine; treatment continued for 2 months. After 2 months of therapy, hyperresponsiveness to both antigens was decreased by approximately 2-fold in patients who received budesonide, which suggests that inhaled budesonide increases tolerance to inhaled allergens and protects against an allergen-induced increase in bronchial hyperresponsiveness. A randomized, placebo-controlled trial[45] evaluated budesonide 400 μg twice daily administered for 6 days in normal subjects to determine the effects of budesonide on

TABLE I. BIS pharmacokinetics in children 3 to 6 years of age[50]

Parameter	Value	95% Confidence interval
F (%)	6.1	4.6-8.1
T_{peak} (min)	10-30	NR
C_{peak} (nmol/L)	2.6	NR
AUC/mg (nmol/L·h/mg)	4.6	NR
V_{ss} (L)	55	45-68
CL_S (mL/min)	536	461-623
$T_{1/2:}$ (h)	2.3	2.0-2.6

F, Total systemic bioavailability; T_{peak}, time to peak plasma concentration; *NR*, not reported; C_{peak}, peak plasma concentration; *AUC/mg*, AUC per milligram nominal dose; V_{SS}, volume of distribution at steady state; CL_s, total systemic clearance; $T_{1/2}$, terminal elimination half-life.

the dose-response curves to inhaled leukotriene D_4 (LTD_4) and methacholine. Compared with placebo, budesonide significantly ($P < .05$) reduced the maximal degree of airway narrowing because of LTD_4 and protected the subjects against an LTD_4-induced increase in maximal response to methacholine, without changing the position of the dose-response curves to LTD_4 and methacholine. These findings support the hypothesis that inflammatory changes account for excessive airway narrowing observed in asthma.

Inhaled budesonide diminishes bronchial hyperreactivity in patients with asthma in a dose-dependent manner, and improvement in bronchial hyperreactivity is positively influenced by the duration of the treatment.[46] In a randomized, double-blind trial,[47] children with asthma received either budesonide 200 μg 3 times daily plus salbutamol 200 μg 3 times daily or placebo plus salbutamol 200 μg 3 times daily for 22 months. Between baseline and 4 months of therapy, patients who received salbutamol plus budesonide required an average increase of 0.98 dose steps (doubling dose) of histamine to produce a 20% fall in FEV_1, compared with children who were receiving salbutamol plus placebo therapy and who required a decrease of 0.42 doubling dose of histamine ($P < .0001$).[47] Thus the results indicate a difference of 1.4 doubling dose of histamine between the 2 treatment groups; this difference further increased over time and did not plateau at a median follow-up of 22 months. Similar results were reported in adult patients with asthma who received inhaled budesonide 800 μg twice daily for 6 weeks;[48] this trial demonstrated that changes in FEV_1 plateaued early during budesonide treatment, although hyperresponsiveness to histamine continued to decrease throughout the 6-week period. The clinical relevance of the magnitude of these effects is not certain, but it indicates a reduction in airway sensitivity to irritants.

PHARMACOKINETICS OF BIS

The human pharmacokinetics of budesonide have been evaluated by various routes of administration, including intravenous, oral, pulmonary, nasal inhalation, and rectal. The pharmacokinetic properties of BIS in children are summarized in Table I (data on file, AstraZeneca).

Drug delivery

Nebulizer-compressor combinations have specific and unique characteristics regarding drug output and droplet-size distribution. Aerosol deposition is influenced by droplet size, distribution of the aerosol, inspiratory flow, length of the inspiratory phase, pattern of breathing (nose or mouth breathing),[50] and size and geometry of the airways.[13] Larger droplets are more likely to deposit in the oropharynx, although smaller droplets are more likely to enter the conducting airways and alveoli. Anatomic factors such as a smaller mouth and throat may result in increased drug deposition in the oropharynx; however, the influence of these factors also is dependent on inspiratory flow, which determines the velocity of the droplets entering through nebulization.[13,51]

Numerous nebulizer-compressor systems have been evaluated both in vitro[51] and in vivo[52] to determine total output, delivered dose, respirable mass of the delivered dose, and nebulization time of BIS. Compared with jet nebulizers, ultrasonic nebulizers were inefficient and are not recommended for delivering BIS. BIS must be administered only by a jet nebulizer (data on file, AstraZeneca).

Evidence suggests that jet nebulizer-compressor systems that deliver between 7.2% and 17.8% of the labeled budesonide dose in vitro are expected to deliver a clinically effective dose; these systems are shown in Table II.[51] The nebulizer (Pari LC Jet Plus; Pari Respiratory Equipment, Inc, Richmond, Va) with face mask or mouthpiece with the compressor (Pari Master; Pari Respiratory Equipment, Inc) ranks among the highest with respect to respirable mass of the delivered dose and a short nebulization time.[51] In children with asthma, the Pari LC Jet Plus nebulizer delivers approximately 25% of the labeled BIS dose to the patient; 25% of the remaining dose is delivered to the ambient air, and 50% of the dose stays in the nebulizer. The delivered dose in children is comparable to that in healthy adults (data on file, AstraZeneca).

In a randomized, 5-way crossover trial[53] involving 12 healthy adult volunteers, lung deposition and systemic availability of inhaled budesonide were compared by the use of 3 different nebulizers. The patients received single 2-mg doses of budesonide from the nebulizer (Pari Inhalierboy; Pari Respiratory Equipment, Inc) plus dosimeter (Spira) the Pari LC Jet Plus nebulizer plus Spira dosimeter, and the Maxin MA-2 nebulizer and a 4-mg oral dose and a 0.5-mg intravenous reference dose, with 1-week washout periods between each dose. Lung deposition and systemic availability related to the nominal dose were approximately 15% and 16%, respectively, and did not differ significantly among the 3 nebulizers. In a dose-to-subject analysis, the Pari LC Jet Plus and Maxin MA-2 had similar lung deposition and systemic availability, and both were greater than the Pari Inhalierboy.

Absorption

Budesonide is a nonproteolytic, moderately lipophilic compound with rapid uptake into airway mucosa.[13] After oral administration of budesonide in healthy adults, the

TABLE II. Nebulizer-compressor systems that delivered 7.2% to 17.8% of the labeled budesonide dose in in vitro studies[51]

Nebulizer (distributor)	Compressor (distributor)	Percent of labeled budesonide dose (SD)
Pari LC Jet Plus*	Pulmo-Aide†	17.8 (1.0)
Pari LC Jet Plus*	Pari Master*	16.6 (0.4)
Intertech‡	Pulmo-Aide†	14.8 (2.1)
Baxter Misty-Neb§	Pulmo-Aide†	14.6 (0.9)
Hudson T-Updraft II‖	Pulmo-Aide†	14.6 (1.2)
Hudson T-Updraft II‖	Medi-Mist¶	14.5 (0.9)
Hudson T-Updraft II‖	Hudson‖	14.2 (1.6)
Hudson Ava-Neb‖	Pulmo-Aide†	13.8 (1.2)
Hudson Ava-Neb‖	Medi-Mist¶	13.5 (1.5)
Aiolos#	Medic-Aid CR60**	13.4 (0.9)
Pari LC Jet*	Pari Master*	13.4 (0.8)
Hudson Ava-Neb‖	Hudson‖	12.7 (0.8)
Pari LC Jet*	Pulmo-Aide†	12.5 (1.1)
DeVilbiss Pulmo-Neb†	Pulmo-Aide Traveller†	11.8 (2.0)
Hudson Iso-Neb (B)‖	Hudson‖	11.6 (1.8)
Hudson T-Updraft Neb-U-Mist‖	Hudson‖	11.1 (1.7)
Hudson T-Updraft Neb-U-Mist‖	Medi-Mist¶	11.0 (1.4)
Pari-Jet 1460*	Pro-Neb*	10.1 (0.8)
Pari-Jet 1460*	Dura-Neb 2000*	9.9 (0.4)
DeVilbiss Pulmo-Neb†	Pulmo-Aide†	9.3 (1.4)
AeroTech with T-piece††	Schuko††	9.0 (1.3)
DeVilbiss Pulmo-Neb†	Pulmo-Aide†	7.2 (1.3)

*Pari Respiratory Equipment Inc, Richmond, Va.
†DeVilbiss Health Care Inc, Chicago, Ill.
‡Intertech Resources Inc, Lincolnshire, Ill.
§Baxter Healthcare Corp, Deerfield, Ill.
‖Hudson Respiratory Care, Inc, Temecula, Calif.
¶Mountain Medical Equipment Inc, Denver, Colo.
#Aiolos Medicnsk Teknik AB, Karlstad, Sweden.
**Medic-Aid Ltd, Sussex, UK.
††CIS-US, Bedford, Mass.

peak plasma concentration was reached within approximately 1 to 2 hours, and the absolute systemic availability was 6% to 13%.[7] A variable portion of inhaled corticosteroid is deposited in the oropharynx, and this potentially systemically available drug may result in unwanted systemic effects.[12] The budesonide deposited in the oropharynx is assumed to be swallowed and eventually absorbed from the gastrointestinal tract; however, because of extensive first-pass elimination of oral budesonide (approximately 85%-90%), very little drug is systemically absorbed.[53-55] In 3- to 6-year-old children with asthma, the total systemic availability (pulmonary plus oral) of BIS by a jet nebulizer was approximately 6% of the labeled dose.[49]

The peak plasma concentration of budesonide occurs approximately 10 to 30 minutes after the start of nebulization in children and adults (data on file, AstraZeneca). After nebulization of BIS 1 mg with the Pari LC Jet Plus nebulizer in children 3 to 6 years of age, the peak plasma concentration was approximately 2.6 nmol/L at 17 minutes after the start of nebulization (Fig 3).[49] Systemic exposure, defined as area under the plasma concentration–time curve (AUC) per mg nominal dose, was 4.6 nmol/L·hour per mg in children, compared with 3.9 nmol/L·hour per mg in adults (Fig 4).[49] These data suggest that the systemic availability after inhalation of the same nominal dose from a Pari nebulizer is similar in young children and adults, despite their difference in size and weight. In addition, evidence suggests that systemic exposure to inhaled budesonide (with a pMDI with a metal spacer) in children 2 to 3 years of age is similar to that observed in children 4 to 6 years of age and adults.[56]

Distribution

Budesonide is distributed widely into tissues and is 85% to 90% protein bound over the concentration range of 1 to 100 nmol/L, the latter exceeding the concentrations achieved with recommended doses. Budesonide shows little or no binding to corticosteroid-binding globulin and rapidly equilibrates with red blood cells with a blood/plasma ratio of approximately 0.8, which is independent of concentration.[7] In children 3 to 6 years of age, budesonide has a mean volume of distribution at steady state of approximately 3 L/kg, which is similar to that observed in adults.[49]

Metabolism

In vitro studies with human liver homogenates indicate that budesonide is rapidly and extensively metabolized by the cytochrome P450 system, specifically by CYP3A enzymes.[7,57] The resulting major metabolites of budesonide are 16α-hydroxyprednisolone and 6β-

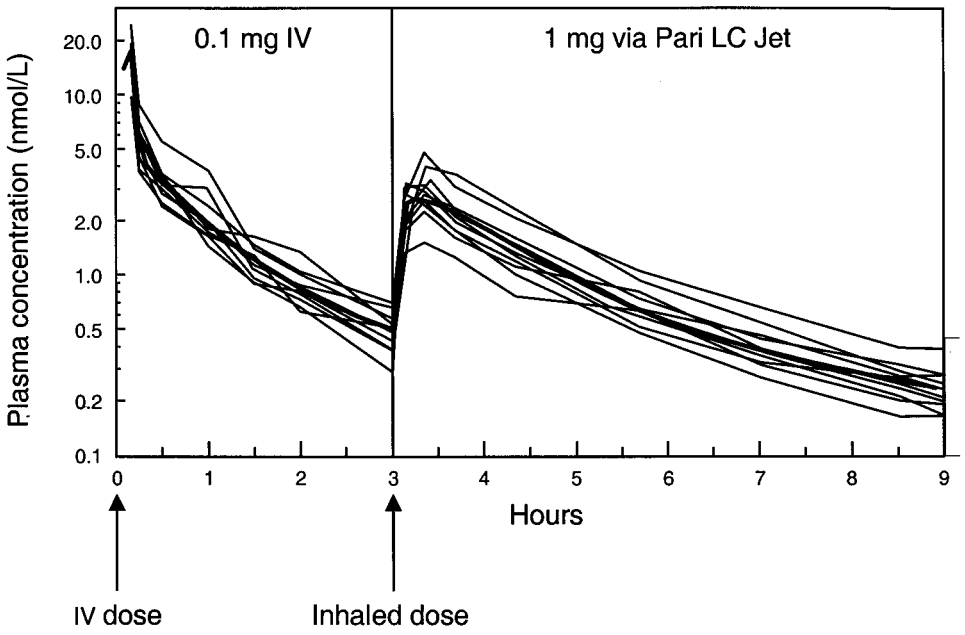

FIG 3. BIS plasma concentration-time data in children 3 to 6 years of age (n = 10). (Adapted from Agertoft L, Andersen A, Weibull E, Pedersen S. Systemic availability and pharmacokinetics of nebulized budesonide in preschool children. Arch Dis Child 1999;80:241-7. With permission from the BMJ Publishing Group.)

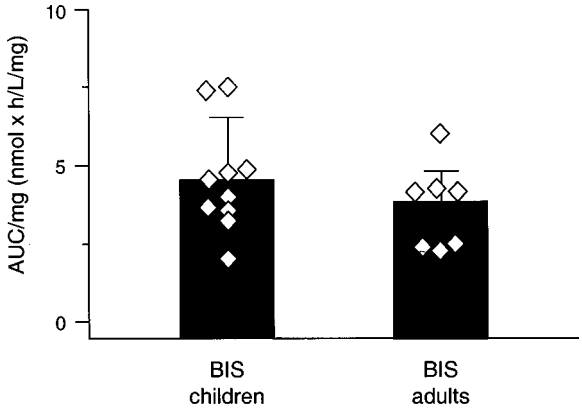

FIG 4. Systemic exposure to inhaled budesonide in children and adults expressed as AUC per milligram of labeled dose. *Diamonds* represent individual data points for each group. (Data on file, AstraZeneca.)

hydroxybudesonide (Fig 1); these metabolites have glucocorticoid-receptor and topical anti-inflammatory activities, which are only 1% or less than that of the parent drug.[7,58-60] No important differences were detected between in vitro and in vivo metabolic patterns, and little metabolic inactivation was observed in human lung and serum studies.[7,54] Budesonide has a high affinity for the lung; a study that used the isolated perfused rat lung model demonstrated that a substantial fraction of budesonide present in the lungs is bound to tissue components and is retained for an extended time period.[61]

Studies in human lung and liver microsomes have demonstrated that esterification of the 16α, 17α-acetal group of budesonide by coenzyme A and adenosine triphosphate leads to the formation of budesonide fatty acid conjugates (Fig 5).[62] In a recent study, the topical uptake and airway retention of radiolabeled budesonide, fluticasone, and beclomethasone dipropionate were compared in rats.[63] Budesonide, fluticasone, and beclomethasone dipropionate were equally well taken up into airway tissue. Budesonide was shown to form lipophilic intracellular fatty acid esters (at the C-21 position) in the airway and lung tissue after topical application. In the large airways, approximately 70% to 80% of retained budesonide was conjugated 20 minutes after administration; conjugated budesonide was retained in the large airways longer than fluticasone or beclomethasone dipropionate, which do not form fatty acid conjugates. Conjugation of budesonide is reversible in vivo, and the conjugates gradually are hydrolyzed by intracellular lipases to free budesonide. The reversible conjugation observed with budesonide may enhance airway selectivity[64] and prolong local anti-inflammatory effects.[63,65] The formation of fatty acid conjugates in human lung tissues recently was demonstrated in vivo.[66] These data may explain why budesonide is effective in the treatment of mild asthma when administered once daily. Budesonide has been approved in several countries for once-daily treatment of mild-to-moderate asthma.

Systemic clearance

An important property of inhaled corticosteroids is rapid plasma clearance after absorption, which minimizes potential systemic effects.[12] In children 3 to 6 years of age

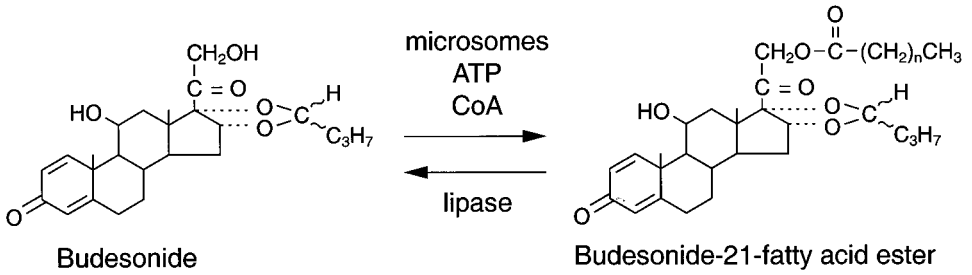

FIG 5. Reversible fatty acid esterification of budesonide.

with asthma, systemic clearance is approximately 30 mL/min/kg, which is approximately 50% greater than that observed in healthy adults, with adjustment for weight differences.[49] High plasma clearance of budesonide in this young population is advantageous to minimize potential systemic adverse effects associated with high-dose treatment.[67] The low-systemic availability of inhaled budesonide and the higher clearance per kilogram of body weight in young children explain why these patients can use the same nebulized budesonide dose as adults without an increased risk of undesirable systemic effects.[49]

Elimination

Budesonide is excreted primarily as metabolites in the urine and feces. Renal elimination of unchanged budesonide is low because of its extensive biotransformation in the liver. In healthy adults, 60% of an intravenous radiolabeled budesonide dose was recovered in urine, and no unchanged budesonide was detected. The terminal elimination half-life of budesonide after inhalation is approximately 2.3 hours in children 3 to 6 years of age with asthma.[7,49]

Compromised liver function may decrease the rate of glucocorticoid elimination.[13] Hepatic impairment increased the systemic availability of budesonide 2-fold after oral ingestion in adults with cirrhosis. However, after intravenous administration, the pharmacokinetics of budesonide were similar in patients with cirrhosis and healthy adults. No differences in the pharmacokinetics of BIS related to race, gender, or advanced age have been identified.

CONCLUSIONS

Budesonide is a potent topical glucocorticoid with a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects when administered by inhalation in patients with asthma. Therapeutic benefits of inhaled budesonide are explained primarily by its local effects in the lung. Inhaled budesonide has been shown to reduce the number of inflammatory cells and mediators present in the airways of patients with asthma. In addition, inhaled budesonide has been shown to decrease airway hyperresponsiveness after histamine, methacholine, and allergen challenges in children with asthma.

The pharmacokinetics of BIS administered by nebulization have been well characterized in children. Only jet nebulizers are recommended for administration of BIS. Absorption of nebulized budesonide from the lungs is rapid, with peak plasma concentrations reached approximately 10 to 30 minutes after the start of nebulization. Budesonide is highly protein bound, undergoes extensive first-pass hepatic metabolism, and is rapidly metabolized by the cytochrome P450 system in the liver. In children 3 to 6 years of age, nebulization of BIS 1 mg with the Pari LC Jet Plus nebulizer resulted in an AUC of 4.6 nmol/L·hour/mg nominal dose; in adults, the AUC was 3.9 nmol/L·hour/mg nominal dose. These data suggest that systemic availability after inhalation of identical nominal doses from a Pari nebulizer is similar in children and adults. The volume of distribution at steady state of BIS is approximately 3 L/kg and the terminal elimination half-life is approximately 2.3 hours in children 3 to 6 years of age. Budesonide is excreted in the urine primarily as metabolites; renal elimination of unchanged budesonide is very low. The corticosteroid activity of the 2 primary budesonide metabolites is less than 1% of the parent compound. Evidence suggests that budesonide fatty acid conjugates are formed and retained in the lung on inhalation; this conjugation is reversible and may prolong anti-inflammatory activity, potentially allowing once-daily dosing.

Overall, the pharmacokinetic profile of BIS allows for a long duration of local therapeutic effects with minimal systemic exposure. This novel formulation of budesonide is a long-awaited therapeutic option for the treatment of persistent asthma in infants and children up to 8 years of age.

REFERENCES

1. Lemanske RF Jr, Busse WW. Asthma. JAMA 1997;278:1855-73.
2. Barnes PJ. Inhaled glucocorticosteroids for asthma. N Engl J Med 1995;332:868-75.
3. National Asthma Education and Prevention Program. Expert panel report 2: guidelines for the diagnosis and management of asthma. Bethesda (MD): NIH/National Heart, Lung, and Blood Institute; 1997. Publication no. 97-4051.
4. Foucard T. Aggressive treatment of childhood asthma with local steroids: Good or bad? Allergy 1996;51:365-71.
5. Brogden RN, McTavish D. Budesonide: an updated review of its pharmacological properties, and therapeutic efficacy in asthma and rhinitis. Drugs 1992;44:375-407.
6. Clissold SP, Heel RC. Budesonide: a preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis. Drugs 1984;28:485-518.
7. Pulmicort Turbuhaler (budesonide inhalation powder) prescribing infor-

mation. Astra Pharmaceuticals, L.P. In: Physicians' desk reference. 53rd ed. Montvale (NJ): Medical Economics Company; 1999. p.587-91.
8. Barnes PJ. Molecular mechanisms of glucocorticoid action in asthma. Pulm Pharmacol Ther 1997;10:3-19.
9. Pedersen S, O'Byrne P. A comparison of the efficacy and safety of inhaled corticosteroids in asthma. Allergy 1997;52(suppl):1-34.
10. Barnes PJ, Adcock I. Anti-inflammatory actions of steroids: molecular mechanisms. Trends Pharmacol Sci 1993;14:436-41.
11. Schleimer RP. Glucocorticosteroids: their mechanisms of action and use in allergic diseases. In: Middleton E, Reed E, Ellis EF, Adkinson NE, Yuninger JW, Busse WW, editors. Allergy, principles and practice. St Louis (MO): Mosby–Year Book, Inc; 1998. p. 638-60.
12. Derendorf H, Hochhaus G, Meibohm B, Möllmann H, Barth J. Pharmacokinetics and pharmacodynamics of inhaled corticosteroids. J Allergy Clin Immunol 1998;101:S440-6.
13. Edsbäcker S, Szefler SJ. Glucocorticoid pharmacokinetics: principles and clinical applications. In: Schleimer R, O'Byrne P, editors. Inhaled corticosteroids in asthma: lung biology in health and diseases series. Lenfant C, editor. vol 97. New York: Marcel Dekker; 1997. p. 381-445.
14. Würthwein G, Rehder S, Rohdewald P. Lipophilicity and receptor affinity of glucocorticoids. Pharm Zeit Wissensch 1992;137:161-7.
15. Thalén A, Brattsand R, Andersson PH. Development of glucocorticosteroids with enhanced ratio between topical and systemic effects. Acta Derm Venereol 1989;69(suppl):11-9.
16. Brattsand R, Thalén A, Roempke K, Källström L, Gruvstad E. Development of new corticosteroids with a very high ratio between topical and systemic activities. Eur J Respir Dis 1982;63(suppl):62-73.
17. Brattsand R, Thalén A, Roempke K, Källström L, Gruvstad E. Influence of 16α, 17α-acetal substitution and steroid nucleus fluorination on the topical to systemic activity ratio of glucocorticoids. J Steroid Biochem 1982;16:779-86.
18. Johansson S-Å, Andersson K-E, Brattsand R, Gruvstad E, Hedner P. Topical and systemic glucocorticoid potencies of budesonide, beclomethasone dipropionate and prednisolone in man. Eur J Respir Dis 1982;63(suppl):74-82.
19. Johansson S-Å, Andersson K-E, Brattsand R, Gruvstad E, Hedner P. Topical and systemic glucocorticoid potencies of budesonide and beclomethasone dipropionate in man. Eur J Clin Pharmacol 1982;22: 523-9.
20. Phillips GH. Structure-activity relationships of topically active steroids: the selection of fluticasone propionate. Respir Med 1990;84(suppl):19-23.
21. Reed CE. Glucocorticosteroids in asthma. Immunol Allergy Clin North Am 1993;13:903-15.
22. Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johansson S-A. Bioequivalent doses of budesonide and prednisone in moderate and severe asthma. J Allergy Clin Immunol 1989;84:688-700.
23. Löfdahl C-G, Mellstrand T, Svedmyr N. Glucocorticoids and asthma: studies of resistance and systemic effects of glucocorticoids. Eur J Respir Dis 1984;65(suppl):69-79.
24. Toogood JH, Frankish CW, Jennings BH, Baskerville JC, Borga O, Lefcoe NM, et al. A study of the mechanism of antiasthmatic action of inhaled budesonide. J Allergy Clin Immunol 1990;85:872-80.
25. Djukanovic R, Wilson JW, Britten KM, Wilson SJ, Walls AF, Roche WR, et al. Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma. Am Rev Respir Dis 1992;145:669-74.
26. Marianayagam L, Spiteri M, Poulter LW. Budesonide induces distinct phenotypic changes in alveolar macrophage populations [abstract]. Am Rev Respir Dis 1990;141:A215.
27. Bergstrand H, Björnsson A, Lundquist B, Nilsson A, Brattsand R. Inhibitory effect of glucocorticosteroids on anti-IgE-induced histamine release from human basophilic leukocytes: evidence for a dual mechanism of action. Allergy 1984;39:217-30.
28. Bergstrand H, Lundquist B, Petersson B-Å. The glucocorticosteroid, budesonide, partially blocks histamine release from human lung tissue *in vitro*. Allergy 1986;41:319-26.
29. Brattsand R, Delander E-L, Peterson C, Wieslander E. Cytotoxicity of human phagocytes studied *in vitro* in a novel model based on Neutral Red absorption. Agents Actions 1991;34:35-7.
30. Cox G, Ohtoshi T, Vancheri C, Denburg JA, Dolovich J, Gauldie J, et al. Promotion of eosinophil survival by human bronchial epithelial cells and its modulation by steroids. Am J Respir Cell Mol Biol 1991;4:525-31.
31. Borson DB, Gruenert DC. Glucocorticoids induce neutral endopeptidase in transformed human tracheal epithelial cells. Am J Physiol 1991; 260:L83-9.
32. Burke C, Power CK, Norris A, Condez A, Schmekel B, Poulter LW. Lung function and immunopathological changes after inhaled corticosteroid therapy in asthma. Eur Respir J 1992;5:73-9.
33. Burke CM, Sreenan S, Power CK, Pathmakanthan S, Poulter LW. Mechanism of action of inhaled corticosteroids in bronchial asthma: a controlled study [abstract]. Eur Respir J 1994;7(suppl):421S.
34. Jeffrey PK, Godfrey RW, Ädelroth E, Nelson F, Rogers A, Johansson S-A. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma. Am Rev Respir Dis 1992;145:890-9.
35. Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a β2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. J Allergy Clin Immunol 1992;90: 32-42.
36. Juniper EF, Frith PA, Hargreave FE. Long-term stability of bronchial responsiveness to histamine. Thorax 1982;37:288-91.
37. Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Comparison of a β_2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. N Engl J Med 1991; 325:388-92.
38. Juniper EF, Kline PA, Vanzieleghem MA, Hargreave FE. Reduction of budesonide after a year of increased use: a randomized controlled trial to evaluate whether improvements in airway responsiveness and clinical asthma are maintained. J Allergy Clin Immunol 1991;87:483-9.
39. O'Connor BJ, Evans PM, Ridge SM, Fuller RW, Barnes PJ. Effect of an inhaled steroid (budesonide) on indirect airway responsiveness (AR) and eosinophils in asthma [abstract]. Am Rev Respir Dis 1991;143:A422.
40. Vathenen AS, Knox AJ, Wisnieski A, Tattersfield AE. Time course of change in bronchial reactivity with an inhaled corticosteroid in asthma. Am Rev Respir Dis 1991;143:1317-21.
41. Gauvreau GM, Doctor J, Watson RM, Jordana M, O'Byrne PM. Effects of inhaled budesonide on allergen-induced airway responses and airway inflammation. Am J Respir Crit Care Med 1996;154:1267-71.
42. Kidney JC, Boulet L-P, Hargreave FE, Deschesnes F, Swystun VA, O'Byrne PM, et al. Evaluation of single-dose inhaled corticosteroid activity with an allergen challenge model. J Allergy Clin Immunol 1997;100:65-70.
43. Paggiaro PL, Dente FL, Morelli MC, Bancalari L, Di Franco A, Giannini D, et al. Postallergen inhaled budesonide reduces late asthmatic response and inhibits the associated increase of airway responsiveness to methacholine in asthmatics. Am J Respir Crit Care Med 1994;149:1447-51.
44. De Baets FM, Goeteyn M, Kerrebijn KF. The effect of two months of treatment with inhaled budesonide on bronchial responsiveness to histamine and house-dust mite antigen in asthmatic children. Am Rev Respir Dis 1990;142:581-6.
45. Bel EH, van der Veen H, Dijkman JH, Sterk PJ. The effect of inhaled budesonide on the maximal degree of airway narrowing to leukotriene D_4 and methacholine in normal subjects in vivo. Am Rev Respir Dis 1989;139:427-31.
46. Kraan J, Koëter GH, Van der Mark ThW, Boorsma M, Kukler J, Sluiter HJ, et al. Dosage and time effects of inhaled budesonide on bronchial hyperreactivity. Am Rev Respir Dis 1988;137:44-8.
47. van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Pocock SJ, Kerrebijn KF, et al. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. Am Rev Respir Dis 1992;146:547-54.
48. Vathenen AS, Knox AJ, Wisnieski A, Tattersfield AE. Effect of inhaled budesonide on bronchial reactivity to histamine, exercise, and eucapnic dry air hyperventilation in patients with asthma. Thorax 1991;46:811-6.
49. Agertoft L, Andersen A, Weibull E, Pedersen S. Systemic availability and pharmacokinetics of nebulized budesonide in preschool children. Arch Dis Child 1999;80:241-7.
50. Everard ML, Hardy JG, Milner AD. Comparison of nebulized aerosol deposition in the lungs of healthy adults following oral and nasal inhalation. Thorax 1993;48:1045-6.
51. Smaldone GC, Cruz-Rivera M, Nikander K. In vitro determination of inhaled mass and particle distribution for budesonide nebulizing suspension. J Aerosol Med 1998;11:113-25.

52. Lödrup Carlsen KC, Nikander K, Carlsen K-H. How much nebulized budesonide reaches infants and toddlers? Arch Dis Child 1992;67:1077-9.
53. Dahlström K, Larsson P. Lung deposition and systemic availability of budesonide inhaled as a nebulised suspension from different nebulizers [abstract]. J Aerosol Med 1995;8:47.
54. Ryrfeldt Å, Andersson P, Edsbäcker S, Tönnesson M, Davies D, Pauwels R. Pharmacokinetics and metabolism of budesonide: a selective glucocorticoid. Eur J Resp Dis 1982;63(suppl):86-95.
55. Ryrfeldt Å, Edsbäcker S, Pauwels R. Kinetics of epimeric glucocorticoid budesonide. Clin Pharmacol Ther 1984;35:525-30.
56. Anhøj J, Thorsson L, Bisgaard H. The systemic exposure of budesonide inhaled from a metal spacer is similar in young children and adults [abstract]. Eur Respir J 1998;12(suppl):378s.
57. Jönsson G, Åström A, Andersson P. Budesonide is metabolized by cytochrome P450 3A (CYP3A) enzymes in human liver. Drug Metab Dispos 1995;23:137-42.
58. Dahlberg E, Thalén A, Brattsand R, Gustafsson J-Å, Johansson U, Roempke K, et al. Correlation between chemical structure, receptor binding, and biological activity of some novel, highly active, 16α, 17α-acetal-substituted glucocorticoids. Mol Pharmacol 1984;25:70-8.
59. Andersson P, Ryrfeldt Å. Biotransformation of the topical glucocorticoids budesonide and beclomethasone 17α, 21-dipropionate in human liver and lung homogenate. J Pharm Pharmacol 1984;36:763-5.
60. Edsbäcker S, Andersson P, Lindberg C, Paulson J, Ryrfeldt Å, Thalén A. Liver metabolism of budesonide in rat, mouse, and man. Drug Metab Dispos 1987;15:403-11.
61. Ryrfeldt Å, Persson G, Nilsson E. Pulmonary disposition of the potent glucocorticoid budesonide, evaluated in an isolated perfused rat lung model. Biochem Pharmacol 1989;38;17-22.
62. Tunek A, Sjödin K, Hallström G. Reversible formation of fatty acid esters of budesonide, an antiasthma glucocorticoid, in human lung and liver microsomes. Drug Metab Dispos 1997;25:1311-7.
63. Miller-Larsson A, Mattsson H, Hjertberg E, Dahlbäck M, Tunek A, Brattsand R. Reversible fatty acid conjugation of budesonide. Novel mechanism for prolonged retention of topically applied steroid in airway tissue. Drug Metab Dispos 1998;26:623-30.
64. Edsbäcker S, Jendbro M. Modes to achieve topical selectivity of inhaled glucocorticosteroids(focus on budesonide. In: Dalby RN, Byron PR, Farr SJ, editors. Respiratory drug delivery-VI. Buffalo Grove (IL): Interpharm Press, Inc; 1998. p. 71-82.
65. Wieslander E, Delander E-L, Järkelid L, Hjertberg E, Tunek A, Brattsand R. Pharmacologic importance of the reversible fatty acid conjugation of budesonide studied in a rat cell line *in vitro*. Am J Respir Cell Mol Biol 1998;19:477-84.
66. Thorsson L, Thunnisen FBJM, Korn S, Carlshaf A, Edsbäcker S, Wouters EFM. Formation of fatty acid conjugates of budesonide in human lung tissue in vivo [abstract]. Am J Respir Crit Care Med 1998;157:A404.
67. Pedersen S, Steffensen G, Ekman I, Tonnesson M, Borga O. Pharmacokinetics of budesonide in children with asthma. Eur J Clin Pharmacol 1987;31:579-82.