Inhaled Corticosteroids in Lung Diseases

Hengameh H. Raissy[1], H. William Kelly[1], Michelle Harkins[2], and Stanley J. Szefler[3,4,5,6]

[1]Department of Pediatrics and [2]Department of Internal Medicine, School of Medicine, University of New Mexico, Albuquerque, New Mexico; [3]Division of Pediatric Clinical Pharmacology and [4]Division of Allergy and Immunology, Department of Pediatrics, National Jewish Health, Denver, Colorado; [5]Department of Pediatrics and [6]Department of Pharmacology, University of Colorado School of Medicine, Denver, Colorado

Inhaled corticosteroids (ICSs) are used extensively in the treatment of asthma and chronic obstructive pulmonary disease (COPD) due to their broad antiinflammatory effects. They improve lung function, symptoms, and quality of life and reduce exacerbations in both conditions but do not alter the progression of disease. They decrease mortality in asthma but not COPD. The available ICSs vary in their therapeutic index and potency. Although ICSs are used in all age groups, younger and smaller children may be at a greater risk for adverse systemic effects because they can receive higher mg/kg doses of ICSs compared with older children. Most of the benefit from ICSs occurs in the low to medium dose range. Minimal additional improvement is seen with higher doses, although some patients may benefit from higher doses. Although ICSs are the preferred agents for managing persistent asthma in all ages, their benefit in COPD is more controversial. When used appropriately, ICSs have few adverse events at low to medium doses, but risk increases with high-dose ICSs. Although several new drugs are being developed and evaluated, it is unlikely that any of these new medications will replace ICSs as the preferred initial long-term controller therapy for asthma, but more effective initial controller therapy could be developed for COPD.

Keywords: asthma; asthma control; asthma guidelines; β-adrenergic agonists; corticosteroids

HISTORICAL PERSPECTIVE

Corticosteroids are widely used in the treatment of lung diseases. Their efficacy comes from their broad antiinflammatory and immunosuppressive effects. Systemic corticosteroids were first shown to be effective in the treatment of acute asthma in 1956 (1). Since then, numerous studies have confirmed the effectiveness of systemic corticosteroid therapy in managing acute and chronic asthma. Since the mid-1990s, several studies have demonstrated their efficacy in acute exacerbations of chronic obstructive pulmonary disease (COPD) (2).

Beclomethasone dipropionate (BDP) was introduced in the early 1970s as the first inhaled corticosteroid (ICS) to show enhanced topical to systemic activity (i.e., therapeutic index) (3). Subsequently, studies have documented the effectiveness and limited adverse effects of ICSs for decreasing morbidity and mortality from asthma (4, 5). However, ICS therapy in COPD has been controversial (6, 7). Six ICSs are available for use in the United States: BDP, flunisolide, budesonide (BUD), fluticasone propionate (FP), mometasone furoate, and ciclesonide.

MECHANISM OF ACTION

Corticosteroids have many cell- and tissue-specific antiinflammatory effects that have been extensively described (8). The corticosteroid enters the cell cytoplasm and binds with the inactive glucocorticoid receptor complex. Consequently, the activated glucocorticoid receptor binds to DNA at the glucocorticoid response element sequence and promotes synthesis of antiinflammatory proteins (transactivation) and inhibits transcription and synthesis of many proinflammatory cytokines (transrepression) (8). Transactivation is also responsible for many adverse systemic effects of corticosteroids. Corticosteroids also reduce the number of T lymphocytes, dendritic cells, eosinophils, and mast cells in airways and reduce inducible nitric oxide production (8).

PHARMACOKINETICS

The pharmacokinetics and pharmacodynamics of the available ICSs have been extensively reviewed elsewhere (9–11). Table 1 presents the factors that determine "clinically comparable doses" for efficacy and the therapeutic index of the ICSs. The delivery device can alter efficacy and therapeutic index (9–12). Therapeutic index is improved by decreased oral bioavailability, increased systemic clearance, and prolonged residence time in the lung secondary to increased lipophilicity, which results in increased volume of distribution (Table 1) (9–11). Even ICSs with a greater therapeutic index produce systemic effects when administered in the high-dose range as defined by the guidelines (Table 2) (4).

Younger and smaller children may be at a greater risk for adverse systemic effects because they can receive higher mg/kg doses of ICSs when administered by metered-dose inhaler (MDI) and valved holding chambers (VHCs), particularly with the newer static free VHCs, compared with older children (13, 14).

PHARMACODYNAMICS

As with other drugs whose mechanisms are receptor mediated, corticosteroids exhibit a log–dose linear effect; thus, the clinical dose response is often described as flat because doubling the dose is relatively ineffective in producing significant changes in outcomes (9, 10, 15). The ICS dose response is further complicated because the various measures of response (lung function, bronchial hyperresponsiveness, asthma symptom control, exacerbations, sputum, and exhalation markers of inflammation) are downstream events from the direct antiinflammatory

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Correspondence and requests for reprints should be addressed to Stanley J. Szefler, M.D., National Jewish Health, 1400 Jackson Street, Room J304 Molly Blank Building, Denver, Colorado 80206. E-mail: szeflers@njhealth.org

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TABLE 1. PHARMACODYNAMIC/PHARMACOKINETIC PROPERTIES OF CURRENTLY AVAILABLE INHALED CORTICOSTEROIDS*

	Determinants of Efficacy			Determinants of Therapeutic Index		
ICS/Dosage	Binding Affinity†	Lung Delivery‡ (%)	Relative Equivalency (μg)§	Oral Bioavailability (%)	Systemic Clearance (*L/h*)	Volumes of Distribution (*L*)
BDP MDI/40 and 80 μg	0.4	50–60	80	20	150	424‖
BUD DPI/90 and 180 μg nebules/250, 500, and 1,000 μg	9.4	15–30	180	11	84	280
		5–8	500			
CIC MDI/80 or 160 μg	0.12	50	80	<1	152	897‖
FLU/80 μg	1.8	68	160	20	58	96
FP MDI/44, 110, and 220 μg	18	20	88	⩽1	66	602
DPI/ 50, 100, and 250 μg		15	100			
MF/110 and 220 μg	23	11	110	<1	53	332

Definition of abbreviations: BDP = beclomethasone dipropionate; BUD = budesonide; CIC = ciclesonide; DPI = dry-powder inhaler; FLU = flunisolide; FP = fluticasone propionate; ICS = inhaled corticosteroid; MDI = metered-dose inhaler; MF = mometasone furoate.

* Data from References 9–11.

† Receptor binding affinities of ICSs relative to dexamethasone equal to 1.

‡ Assuming appropriate inhalation technique.

§ The relative potency is based on clinical efficacy rather than systemic activity.

‖ Distribution volumes are for the active metabolites of BDP and CIC.

effects that have been extensively reviewed (8). Most studies and metaanalyses of the dose response suggest that most of the benefit from ICSs occurs in the low to medium dose range with minimal additional improvement with higher doses, although some patients may benefit from these higher doses (15–18).

Factors associated with a diminished dose response to ICSs include genetic polymorphisms, COPD, smoking, severe asthma, obesity, and vitamin D insufficiency (8, 19–22). Patients with asthma who are homozygous for the variant allele rs37973, which maps to the glucocorticoid-induced transcript 1 gene (*GLCCI1*), show about one third the lung function response of that of those homozygous for the wild-type allele (19). The variant occurs in about 16% of the population. Smoking, COPD, and severe asthma result in oxidative stress and influx of multiple inflammatory cytokines that produce glucocorticoid resistance through a number of heterogeneous molecular mechanisms that have been extensively reviewed (8). Even *in utero* smoke exposure has been associated with diminished response to ICSs in school-aged children (23). There are ongoing prospective clinical trials to determine whether vitamin D supplementation restores ICS responsiveness in patients with insufficiency.

CLINICAL USE

Asthma

The ICSs are the preferred agents for managing persistent asthma in all ages, and the dose is based on the severity and control of the disease (4). ICSs have consistently been shown to improve lung function, decrease bronchial hyperresponsiveness, reduce asthma exacerbations resulting in emergency department visits and hospitalizations, decrease the risk of death, and reduce the need for as-needed short-acting β_2 agonists and oral corticosteroids in all age groups. However, they do not alter the natural progression of the disease (4, 24, 25).

Comparative clinical trials in children as young as 2 years of age and adults show that ICSs are more effective than nonsteroid, long-term controllers (25, 26). Chronic administration of ICSs also reduces exercise-induced bronchospasm in children more effectively and consistently as compared with leukotriene modifiers (27).

COPD

Long-term treatment with ICSs is recommended by the GOLD guidelines for patients with an FEV_1 <50% predicted and/or

TABLE 2. COMPARATIVE DAILY DOSAGES OF INHALED CORTICOSTEROIDS*

Corticosteroid	Low Daily Dose (μg, *Child*†/*Adult*)	Medium Daily Dose (μg, *Child*†/*Adult*)	High Daily Dose (μg, *Child*†/*Adult*)
BDP			
HFA MDI	80–160/80–240	>160–320/>240–480	>320/>480
BUD			
DPI	180–360/180–540	>360–720/>540–1,080	>720/>1,080
Nebules	500/UK	1,000/UK	2,000/UK
CIC	80–160/160–320	>160–320/>320–640	>320/>640
FLU			
HFA MDI	160/320	320/320–640	>640/>640
FP			
HFA MDI	88–176/88–264	>176–352/>264–440	>352/>440
DPIs	100–200/100–300	>200–400/>300–500	>400/>500
MF, DPI	110/220	220–440/440	>440/>440

Definition of abbreviations: BDP = beclomethasone dipropionate; BUD = budesonide; CIC = ciclesonide; DPI = dry-powder inhaler; FLU = flunisolide; FP = fluticasone propionate; HFA = hydrofluoroalkanes; MDI = metered-dose inhaler; MF = mometasone furoate; UK = unknown.

* Data from Reference 4.

† Five to 11 yr of age, except for BUD nebules (2–11 yr of age).

frequent exacerbations and whose symptoms are not adequately controlled on long-acting bronchodilators, although long-term monotherapy with ICS is not recommended (7). No clinical factors have been identified that can predict ICS responsiveness and long-term safety, and ultimate dosing is unknown (6, 28). Regular treatment with ICSs in patients with COPD improves symptoms, lung function, and quality of life measures and reduces exacerbations in patients with FEV_1 <60% compared with placebo (6, 28, 29). A metaanalysis of 13,000 patients with COPD found no effect of ICSs on the rate of decline in FEV_1 or in mortality; however, they have been shown to reduce exacerbation rate by 25% (28). However, these studies used high-dose ICSs (1,000 μg/d FP or comparable) that would expose the patients to increased risk of systemic adverse effects (5, 8).

Dosing Strategies

All of the current ICSs are more effective when administered twice daily in moderate to severe asthma; however, they have been shown to control mild asthma with once-daily dosing (9). The issue of improving compliance with once-daily administration of the ICSs remains to be evaluated in controlled clinical trials.

In patients with mild or intermittent asthma, the use of ICSs as needed with rescue bronchodilator or intermittently at high doses for a prescribed duration (5–10 d) has been investigated in pediatric and adult populations (30–35). These studies have been inconsistent and confirm greater efficacy of daily use of ICSs for controlling the impairment domain and mixed effects on preventing exacerbations requiring oral corticosteroids (30–35). Although the combination BUD with the long-acting β_2 agonist (LABA) formoterol in a single inhaler has been approved in Europe and other countries for maintenance and reliever therapy, it has not been approved for this use in the United States, and recently concerns have been expressed that patients receiving this therapy are not well controlled and may have inadequately treated airways inflammation (30). The use of intermittent ICS therapy for preschool children with viral-induced wheezing is of particular interest (36–38). Two recent trials suggest that intermittent high-dose use is as effective as continuous low-dose therapy and placebo in infants and young children (37, 38). However, the children in the latter trial who received very-high-dose FP (1.5 mg/d via MDI plus VHC) experienced systemic effects of weight and growth retardation (38), whereas the children who received high-dose BUD (2.0 mg/d via jet nebulization) did not (37). Thus, optimal dosing for this strategy needs to be determined.

It has been posited that the newer, small-particle–generating (or ultrafine particle) ICS MDIs may provide enhanced control because of their improved delivery to the peripheral small airways (39, 40). It has been well documented that small airways (<2 mm diameter) inflammation results in increased air trapping and bronchial hyperresponsiveness and is associated with increased nocturnal asthma and severe uncontrolled asthma phenotypes (39–42). Small airways dysfunction is also common in COPD (41, 42). Although initial investigations in small numbers of patients have demonstrated preferential improvement in some measures of small airways disease, results have been inconsistent and confounded by differential dosing of the ultrafine versus standard particle delivery devices and study design flaws (40, 41). In addition, large-scale studies comparing ultrafine and standard-particle ICSs have failed to demonstrate improved asthma outcomes for the ultrafine devices when administered in the clinically comparable doses (Table 2), although this may be due to the inclusion of patients that do not have significant small airways disease (39, 40). Improved methods of measuring small airways disease and large-scale trials targeted at patients with significant small airways inflammation are required to determine if targeted therapy provides clinically relevant improvement in asthma and COPD control (39–42).

Cost Effectiveness

Single-entity ICS controller therapy has been shown to be more cost effective than other controllers (leukotriene modifiers, theophylline, and LABAs in a managed care setting and for mild persistent asthma in developing countries) (43, 44). These "real-world" findings are consistent with those seen in structured randomized clinical trials (45). In more moderate to severe asthma, combination therapy with ICS/LABA is more cost effective (46). Cost effectiveness evaluations for medications in COPD are much more complicated due to the small incremental improvements in outcomes compared with those seen in asthma, so that cost effectiveness is determined by willingness to pay (44, 47). Single-entity ICSs are the least cost effective compared with LABAs or ICS/LABA combination, which is mostly attributable to the LABA component (47, 48).

Combination Therapy

The addition of adjunctive therapies is an alternative to increasing the dose of ICS in patients who are inadequately controlled on low to medium doses (4). The combination of ICS/LABA produces improved control and reduced exacerbations, requiring oral corticosteroids compared with increasing the ICS dose in adults with asthma (49). The addition of a LABA in children 4 to 11 years of age improves overall asthma control compared with increasing the ICS dose but does not have a clear benefit on reducing exacerbations (49, 50). The combination of ICS/LABA has not been evaluated in children younger than 4 years of age. The addition of LABAs is superior to the addition of leukotriene modifiers to ICS (51). The effect of adding a LABA on reducing exacerbations (thought to be an antiinflammatory effect) may be explained by a pharmacodynamic interaction allowing the combination to activate the GR at lower ICS doses (52). A primary question surrounding the use of ICS/LABA combinations in the United States is whether the ICS component prevents the rare, life-threatening exacerbations associated with monotherapy with LABAs (53). This is controversial because metaanalyses do not show an increased risk of life-threatening exacerbations with concomitant administration of ICS with LABA (54). This question is being addressed with several large, international US Food and Drug Administration–mandated, randomized clinical trials in children and adults (53).

As opposed to asthma, the question in COPD is whether the ICS adds significantly to the LABA or long-acting muscarinic antagonist. Combination ICS/LABA therapy is modestly more effective than LABAs in improving quality of life, FEV_1, dyspnea, and symptoms and in reducing rescue medication use, but there was a low quality of evidence for exacerbation reduction and no effect on hospitalizations or mortality (55). There is insufficient evidence to assess whether the addition of tiotropium bromide to ICS/LABA improves outcomes other than slightly improved lung function (56).

Measuring Effects and Outcomes

Improvement in prebronchodilator FEV_1, morning and evening peak expiratory flows, bronchial hyperresponsiveness, symptoms, and rescue medication use are standard outcome measures in the impairment domain with prevention of exacerbations in the risk domain (4). Biomarkers of inflammation, such as fraction of exhaled nitric oxide (FeNO), sputum eosinophils, serum eosinophil cationic protein, and exhaled breath condensates, have been advocated as outcome measures; however, each has drawbacks, including not

predicting overall asthma control or not predicting the risk of exacerbations (57, 58). Increasingly, asthma control days or episode-free days that are defined as a day without symptoms or rescue bronchodilator use have been used as an outcome measure for comparative studies (50, 59). The measurement of asthma control days may be more sensitive than lung function changes to dosing changes with ICSs and may be more clinically relevant (15, 57, 59).

When ICSs are initiated, significant improvement in symptoms occurs in 1 to 2 weeks, lung function improvement occurs within the first weeks, and a decrease in FeNO occurs within a few days (57). The maximum symptom improvement usually occurs in 1 to 2 months and maximum lung function improvement in 3 to 6 weeks after treatment. Improvement in bronchial hyperresponsiveness can occur within a few weeks but may continue over months after start of therapy (57).

Due to the rapid onset and offset responses of FeNO to ICS therapy in asthma, it has been used in clinical trials to monitor asthma control and compare ICSs with other conventional therapies (39, 40, 57, 58). Monitoring FeNO in addition to lung function and asthma symptoms has been investigated in pediatric and adult trials, with variable results (60–62). Its greatest utility appears to be in monitoring ICS compliance in difficult-to-control asthma (63).

Adverse Effects

When used appropriately, ICSs have few adverse events at low and medium doses (5). The local side effects result from the deposition of the ICS in the oropharynx and include hoarseness, candidiasis, cough, and dysphonia (4, 5). Potential systemic side effects of ICSs include suppression of the hypothalamus-pituitary-adrenal (HPA) axis, Cushing syndrome, osteoporosis, cataracts, dermal thinning and bruising, adrenal insufficiency, and growth suppression in children (4, 5). Cushing syndrome and associated adrenal insufficiency have been reported with high doses of ICSs or as a result of drug interaction with CYP3A4 inhibitors (64, 65). Additionally, ICS therapy increases the risk of pneumonia in patients with COPD (6, 55).

Several methods have been used to measure HPA axis function with 24-hour serum area-under-the-curve cortisol, low-dose adrenocorticotropin stimulation, and 24-hour and overnight urinary free cortisol being the most sensitive indicators of exogenous corticosteroid exposure (5, 66). The standard test to evaluate the full integrity of the HPA axis is insulin-hypoglycemic stimulation, but standard-dose adrenocorticotropin stimulation has been used for regulatory purposes (66). Although 24-hour urinary cortisol excretion has been approved to compare relative systemic activity from the ICSs, the degree of suppression does not correlate with risk of adrenal insufficiency (58, 66). Patients exposed to high doses of ICSs (based on guidelines; Table 2) should have their HPA axis monitored (65).

Reduced bone mineral density and increased risk of fracture have been reported in older patients on high doses of ICSs (5). Patients with COPD have increased risk factors, including smoking, vitamin D insufficiency, and immobility; furthermore, the doses of ICSs currently used are in the high-dose range (6, 67). Recent analyses of prospective trials of ICSs in COPD have not demonstrated an increased bone mineral density decline or an increased risk of fractures (67). However, as many as 60% of patients with COPD, particularly patients with more severe disease, may have osteoporosis, so bone mineral density measures should be considered. In children, medium doses of BUD for 4 to 6 years did not result in increased risk of osteoporosis or fractures (68). Elderly patients and patients with severe COPD receiving high-dose ICSs should receive appropriate prophylaxis with vitamin D and calcium. Similar to osteoporosis, the risk of cataracts has been reported to be associated with dose and duration of ICSs in elderly patients; however, a long-term prospective trial of 4 to 6 years plus an additional 8-year follow-up with continuous and intermittent therapy did not find an association between ICSs and cataracts (69).

A major concern for ICS therapy in young children is the effect on growth (4, 5, 70). A recent publication reported that the growth suppression seen in the first few years of therapy, although it was dose-dependent and not cumulative, persisted into adulthood (71). Growth suppression is dose and device dependent and has been reported with low to medium doses of BDP MDI (34) and BUD dry-powder inhaler (DPI) (70, 71) in children 4 to 17 years of age and in infants 2 years of age or younger with FP MDI plus VHC (14) but not with low- to medium-dose FP DPI, mometasone furoate DPI, or ciclesonide MDI (71). Several large studies have shown that ICS alone or in combination is associated with increased pneumonia risk and even death from pneumonia, with a dose-related risk (28, 55, 72, 73).

Safety Systems

Although aerosol delivery of ICSs to the lungs improves the safety in patients with asthma and COPD, careful selection of dosage, delivery system, and formulations may further improve their therapeutic index. Although VHCs may be used with MDI for patients who cannot coordinate actuation and inhalation, they can alter the therapeutic index, particularly the newer antistatic devices (9–14). Patients with increased risk for certain adverse effects, such as elderly patients with an increased risk for osteoporosis and cataracts, should be monitored regularly if receiving high doses of ICSs (Table 2). Children on ICSs should have their height measured regularly, and patients with COPD should be monitored for symptoms of pneumonia and receive appropriate influenza and pneumococcus vaccines.

Drug Interactions

All of the current ICSs should be used cautiously with potent inhibitors of cytochrome P450 3A4 isoenzymes (CYP 3A4), such as ritonavir, itraconazole, and ketoconazole (9–11). They are all extensively metabolized by intestinal and hepatic CYP 3A4, which affects their systemic availability and clearance. Adrenal suppression, Cushing syndrome, and death have been reported with coadministration of these agents (64, 74).

Guidelines

Existing data from numerous clinical trials support the current recommendations from national and global asthma and COPD guidelines (4, 7, 75). The asthma guidelines identify ICSs as the preferred long-term controller therapy and the cornerstone of asthma management. They are safe and effective at low to medium doses, but the risk of adverse effects increases with high-dose ICS therapy (4, 75). The COPD guidelines recommend ICS only for patients with severe impairment and high risk of exacerbations but temper it with the need for more studies (7).

Future Developments

New ICSs with prolonged activity for once-daily dosing even in patients with more moderate to severe asthma are undergoing clinical trials in asthma and COPD with and without a once-daily LABA (76, 77). A number of single-mediator inhibitors are being developed, although it is unlikely that any of these new medications will replace ICSs as the preferred initial long-term controller therapy. Efforts are being directed to developing nanoparticle-size ICS formulations that will improve topical delivery to the lung and address peripheral airway disease while minimizing systemic absorption. In addition, numerous compounds isolate the transrepression activity from transactivation are being

developed in hopes of eliminating many of the unwanted systemic effects from ICSs while maintaining antiinflammatory activity (8, 78). Both strategies are intended to increase the therapeutic index of the available ICS.

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