

Pulmonary

Comparison of Inhaled Corticosteroids: An Update

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Inhaled corticosteroids remain the most effective antiinflammatory therapy for the treatment of persistent asthma. The new US National Institutes of Health, National Asthma Education and Prevention Program's Guidelines for the Diagnosis and Management of Asthma, Expert Panel Report 3 (EPR3) has stated that the efficacy of low- to medium-dose inhaled corticosteroid therapy outweighs any small risks of adverse effects.¹ Thus, inhaled corticosteroids are listed as preferred monotherapy for mild-to-moderate persistent asthma for patients of all ages and as baseline therapy with various adjunctive therapies for more severe or difficult-to-control disease. The EPR3 has updated the relative clinical comparability inhaled corticosteroid dose chart (Table 1)²⁻⁷ that was first established in the EPR2, published in 1997.⁸ The changes in the dose chart were based on the introduction of new entities (eg, mometasone furoate), as well as significant formulation changes of older drugs (eg, beclomethasone dipropionate) and additional data from comparative clinical trials.

In 1998, *The Annals* published a comprehensive review of the scientific rationale supporting the comparative inhaled corticosteroid dosing chart in EPR2.⁹ The present report reviews the data supporting the changes found in the EPR3

OBJECTIVE: To review the basis for the estimated comparative daily dosages of inhaled corticosteroids for children and adults that are presented in the National Heart, Lung, and Blood Institute's Expert Panel Report 3; in addition, the pharmacodynamic and pharmacokinetic basis for potential clinical differences among inhaled corticosteroids is discussed.

DATA SOURCES: A complete MEDLINE search was conducted of human studies of asthma pharmacotherapy published between January 1, 2001, and March 15, 2006, followed by a PubMed search up until August 2008, using ciclesonide, inhaled corticosteroids, and pharmacokinetics as key words. Product information on each inhaled corticosteroid was also included.

STUDY SELECTION AND DATA EXTRACTION: Comparative clinical trials of inhaled corticosteroids and systematic reviews for efficacy comparisons were evaluated. Extensive literature reviews, meta-analyses, and selected clinical studies that illustrate or represent specific points of view were selected. Pharmacodynamic and pharmacokinetic data extracted from previously published reviews and specific studies were included.

DATA SYNTHESIS: Pharmacodynamic characteristics (glucocorticoid receptor binding) and lung delivery determine the relative clinical efficacy and pharmacokinetic properties (oral bioavailability, lung retention, systemic clearance) and determine comparative therapeutic index of the inhaled corticosteroids. Secondary pharmacokinetic differences (intracellular fatty acid esterification, high serum protein binding) that have been posited to improve duration of action and/or therapeutic index are unproven, and current comparative clinical trials do not support the hypotheses that they provide an advantage. Ultrafine particle meter-dose inhalers (MDIs) have not demonstrated superior asthma control or improved safety over older MDIs. All of the inhaled corticosteroids demonstrate efficacy with once-daily dosing, and all are more effective when dosed twice daily.

CONCLUSIONS: Current evidence suggests that all of the inhaled corticosteroids have sufficient therapeutic indexes to provide similar efficacy and safety in low to medium doses. Whether or not some of the newer inhaled corticosteroids offer any advantages at higher doses has yet to be determined.

KEY WORDS: asthma, inhaled corticosteroids, pharmacodynamics, pharmacokinetics.

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dosing chart. In addition, data supporting comparable dosing of ciclesonide, an inhaled corticosteroid recently approved by the Food and Drug Administration (FDA), are included. Therefore, this is not a comprehensive review of every inhaled corticosteroid, but rather, an update. Some of the references in this article are extensive reviews.⁹⁻¹⁴ This update should provide clinicians with the background necessary to assess characteristics of the inhaled corticosteroid preparations that are likely to produce clinically significant differences between products. For the purposes of this update and the dosing charts, the doses of each inhaled corticosteroid are those approved by the FDA: for metered-dose inhalers (MDIs), the amount of actuated dose that reaches the patient's mouth; for dry-powder inhalers (DPIs), the amount available in the dose chamber of the device following actuation; and for jet nebulization (NEB), the amount placed in the nebulizer.

Relative Potency of Inhaled Corticosteroids

It has been well established that chemical changes in the basic corticosteroid molecule produce significant differences in potency, usually measured as binding affinity at the glucocorticoid receptor. The relative receptor affinities are provided in Table 2.^{2,7,9-14} The affinities have been compiled from numerous sources and compared with dexamethasone, which is given the arbitrary unit of 1. The rela-

tive binding affinities should not be interpreted as absolute differences in potency, as it is possible to have compounds with high binding affinity but without efficacy. Therefore, numerous laboratories also assess functional activity such as stimulation and suppression of gene activation; however, these studies also provide results that vary between laboratories.^{15,16} The relative binding affinities correlate with relative potencies in carefully controlled clinical trials.¹⁷ It is clear from the relative potencies that some drugs (beclomethasone dipropionate, ciclesonide) act as prodrugs and that their active metabolites (beclomethasone monopropionate and desisobutyl-ciclesonide [des-ciclesonide]) provide most, if not all, of the clinical activity.

Potency does not affect the therapeutic index (topical efficacy to systemic activity ratio), and efficacy differences are simply overcome by administering equipotent doses.^{1,2,9-14} However, potency does determine the efficacy of specific doses and so is one of the major determinants of the relative comparable doses shown in Table 1, along with delivery to the lung from the aerosol device.¹ The best test for comparing clinical potency would be a sensitive measure of asthma inflammation or activity that responded to at least a 2-fold difference in dosing and administration by delivery devices that deliver the same amount of drug in a uniform fashion. Unfortunately, we have neither of these conditions when comparing relative efficacy of the inhaled corticosteroids. For example, using the standard measures

Table 1. Clinically Comparable Doses of Inhaled Corticosteroids

Drug	Comparative Daily Dosages (µg) ^{1,a}					
	Low		Medium		High	
	Child	Adult	Child	Adult	Child	Adult
Beclomethasone dipropionate						
HFA-MDI Pas en Suisse	80–160	80–240	>160–320	>240–480	>320	>480
Budesonide Pulmicort®						
DPI	180–400	200–600	>400–800	>600–1200	>800	>1200
nebulizer	500	UK	1000	UK	2000	UK
Ciclesonide ^b Alvesco®						
HFA-MDI	80–160	160–320	>160–320	>320–640	>320	>640
Flunisolide						
CFC-MDI Pas en Suisse	500–750	500–1000	>1000–1250	>1000–2000	>1250	>2000
HFA-MDI	160	320	320	>320–640	≥640	>640
Fluticasone propionate						
HFA-MDI Axotide®	88–176	88–264	>176–352	264–440	>352	>440
DPI	100–200	100–300	>200–400	300–500	>400	>500
Mometasone furoate ^c DPI Asmanex®	110	220	220–440	440	>440	>440
Triamcinolone acetonide CFC-MDI Pas en Suisse	300–600	300–750	>600–900	>750–1500	>900	>1500

CFC-MDI = chlorofluorocarbon-propelled metered-dose inhaler; DPI = dry-powder inhaler; HFA-MDI = hydrofluoroalkane-propelled metered-dose inhaler; MDI = metered-dose inhaler; UK = unknown.

^aChild age is 5–11 years.

^bDoses are not from reference 1; rather, data are based on comparative clinical trials with fluticasone propionate and budesonide with ciclesonide.²⁻⁵

^cChild doses are not from reference 1; rather, data are based on recent approval in children aged 4–11 years and comparative studies with fluticasone propionate, beclomethasone dipropionate, and budesonide.^{6,7}

of efficacy, improvement in baseline lung function and reduction of the risk of asthma exacerbations, it is not possible to distinguish 2-fold differences in doses of the same inhaled corticosteroid delivered with the same aerosol delivery system.¹⁸⁻²¹ Each device (MDI, DPI, NEB) delivers varying amounts of drug to the lungs of the patients, both intradevice (eg, fluticasone propionate DPI vs budesonide DPI) as well as interdevice and intradrag (fluticasone propionate DPI vs MDI).²²⁻²⁴ Also, the addition of spacer devices to MDIs and use of facemasks with MDIs plus spacers or NEBs can substantially alter delivery.²⁴⁻²⁶ Thus, the clinical comparative doses in Table 1 are based on large or multiple direct comparative clinical trials.

Some have argued that the standard measures of improvement in baseline lung function, symptom scores, and prevention of exacerbation are too insensitive to detect real differences in potency. Other measures, such as improvement in bronchial hyperresponsiveness (BHR) to challenges of exercise, methacholine or adenosine monophosphate, or biomarkers of airway inflammation such as fraction of exhaled nitric oxide and sputum eosinophils, have been posited as more sensitive markers of inhaled corticosteroid response.²⁷⁻²⁹ Although the response of these markers to changing doses of inhaled corticosteroids has yet to be fully established,³⁰ inhaled corticosteroids do produce a more rapid response in these measures so they may be useful for short-term screening studies to establish initial doses for comparing these drugs.^{4,27-31} Measures of BHR change rapidly, but they also continue to improve over a long period of inhaled corticosteroid administration.¹ It is likely that the use of numerous markers of efficacy is more

appropriate, as they measure different aspects of asthma response. Sensitive markers of systemic activity, such as short-term growth, 24-hour urinary free cortisol, and 24-hour area under the curve (AUC⁰⁻²⁴) for serum cortisol and serum osteocalcin, have been used to compare the potency of inhaled corticosteroids.^{22,32} However, as these effects are highly dependent on the differences in the delivery and pharmacokinetics between the inhaled corticosteroid preparations, they are not useful for assessing relative potency, but can be used for determining relative systemic availability. The FDA recently began accepting studies using 24-hour urinary free cortisol as a marker to compare relative systemic availability of the inhaled corticosteroids.

Effect of Delivery Devices

Delivery devices, in conjunction with patient technique, are the primary determinants of the dose delivered to the lungs of the patient.^{1,24} Some of the changes in comparable doses in the new guidelines are based simply on changes in the delivery device (ie, budesonide Turbuhaler to budesonide Flexhaler, and flunisolide to a new hydrofluoroalkane [HFA]-propelled MDI) or new delivery information provided to the FDA (triamcinolone acetonide MDI).¹ The clinically comparable doses for all of the MDIs are based on their use without a spacer device, with the exception of fluticasone MDI in children 0–4 years old. How various spacer devices might affect relative comparable dosing has not been assessed. However, unless use of a spacer with an MDI produces a greater than 2-fold change in dose delivered, it is unlikely to make a clinically significant differ-

Table 2. Pharmacodynamic/Pharmacokinetic Properties of Inhaled Corticosteroids^{2,7,9-14}

Drug	Receptor Binding Affinity ^a	Lung Delivery (%)	Protein Binding (%)	Oral Bioavailability (%)	Systemic Clearance (L/h)	Distribution Volume (L)	Half-Life (h)	
							IV	Inhaled
Beclomethasone dipropionate/17-monopropionate ^b	0.4/13.5	50–60	87	20/40	150/120	20/424	0.5/2.7	UK/2.7
Budesonide	9.4	15–30 ^c	88	11	84	280	2.8	2.0
Ciclesonide/desciclesonide ^b	0.12/12.0	50	99/99	<1/<1	152/228	207/897	0.36/3.4	0.5/4.8
Flunisolide	1.8	68	80	20	58	96	1.6	1.6
Fluticasone propionate	18	20 ^c	90	≤1	66	318–859	7.8	14.4
Mometasone furoate	23 ^d	11 ^d	99	<1	53	152	5.0	UK
Triamcinolone acetonide	3.6	22	71	23	45–69	103	2.0	3.6

DPI = dry-powder inhaler; HFA-MDI = hydrofluoroalkane-propelled metered-dose inhaler; IV = intravenous; UK = unknown.

^aReceptor binding affinities are relative to dexamethasone equal to 1.

^bBeclomethasone dipropionate and ciclesonide are prodrugs that are activated in the lung to their active metabolites beclomethasone 17-monopropionate and desciclesonide, respectively.

^cThese values are for the respective DPIs. All other delivery values are for the respective HFA-MDI preparations under ideal conditions in older children and adults. Actual deliveries are highly patient dependent. The fluticasone propionate DPI delivers 15%; budesonide inhalation suspension delivers 5–8%, depending on the nebulizer.

^dMometasone furoate studied in a different receptor system. Value estimated from relative values of beclomethasone dipropionate, triamcinolone acetonide, and fluticasone propionate in that system.

ence in efficacy. On the other hand, use of a spacer device may alter the systemic availability of an inhaled corticosteroid sufficiently to alter the therapeutic index.²²⁻²⁶ For example, studies using chlorofluorocarbon (CFC)-propelled MDIs of beclomethasone dipropionate and fluticasone propionate have shown that use of a valved holding-chamber (VHC) spacer device decreased systemic activity of beclomethasone dipropionate by decreasing the amount of drug absorbed orally and increased the systemic activity of fluticasone propionate by increasing the amount delivered to the lung.^{22,33} Most of the new inhaled corticosteroid HFA-MDIs have not been adequately studied clinically with VHCs, although some have been assessed with use of *in vitro* models.

The ongoing phase-out of CFC-propelled MDIs has spurred the development of many of the newer devices. Although the FDA required only albuterol CFC-MDIs to be phased out by December 2008, many manufacturers are phasing out their inhaled corticosteroid CFC-MDIs as well. The first inhaled corticosteroid HFA-MDI was beclomethasone dipropionate. Because that drug is soluble in HFA, a new MDI was developed that could produce particles with a much smaller mass median aerodynamic diameter of 1.1 μm , compared with 3.5–4.0 μm of the beclomethasone dipropionate suspensions in CFC-MDIs; this change significantly enhanced lung delivery of the drug.³⁴ The other inhaled corticosteroids in HFA-MDIs, also in solution, include ciclesonide and flunisolide (approved, but not currently available on the market). By contrast, fluticasone propionate is not soluble in HFA, so its HFA-MDI delivers slightly less fluticasone propionate compared with its CFC-MDI.^{35,36} The 4- to 10-fold increase in lung delivery of beclomethasone dipropionate HFA-MDI translated into an only 2.6-fold increase in efficacy for improving lung function over the CFC-MDI in a large dose-response study.³⁷⁻³⁹ This relative efficacy ratio holds up in trials comparing one-half the microgram dose of beclomethasone dipropionate by HFA-MDI with CFC-MDI and similar microgram doses of beclomethasone dipropionate by HFA-MDI with fluticasone propionate CFC-MDI.^{34,40-42}

It has been suggested, but not proven, that the extrafine particles produced by HFA-MDIs of inhaled corticosteroids that are available as solutions may improve outcomes in patients as a result of greater penetration into the peripheral airways.³⁴ However, proving this hypothesis is difficult for 2 reasons: (1) the large increase in total lung delivery produced by the HFA-MDIs masking a specific increase in small airways delivery, and (2) the difficulty in specifically measuring small airways effects to distinguish between those and total effect. Two studies compared beclomethasone dipropionate HFA-MDI with fluticasone propionate administered by DPI in equal microgram daily doses.^{43,44} Although each study concluded that HFA-MDI

had greater efficacy in the small distal airways, they reported conflicting results of efficacy in lung function and the reduction in indices of airway inflammation (blood eosinophils and eosinophil cationic protein, and sputum levels of each). Fluticasone propionate administered by DPI delivers only 10–15% of the dose, which is much lower than even the fluticasone propionate MDI dose, so these small differences could be just a result of differences in total delivery of drug.

Another open-label study compared equal microgram amounts of beclomethasone dipropionate HFA-MDI ($n = 20$) with fluticasone propionate CFC-MDI ($n = 10$) in adults with poorly controlled asthma.⁴⁵ The addition of beclomethasone dipropionate HFA-MDI, but not fluticasone propionate CFC-MDI, increased measures of small airways function, including closing volumes and residual volumes as well as forced expiratory flow over 25–75% of vital capacity. However, forced expiratory volume in 1 second (FEV_1) was also differentially improved, so it is not clear whether this is a specific small-airways effect or just greater total delivery. A more recent crossover comparison of beclomethasone dipropionate HFA-MDI 200 μg daily with fluticasone propionate DPI 200 μg daily in children aged 6–12 years failed to detect a difference in alveolar nitric oxide and bronchial nitric oxide flux, which are measures of small airways inflammation, as well as lung function measures.⁴⁶ Thus, improved small airways delivery resulting in improved overall efficacy of extrafine particle inhaled corticosteroid preparations remains a logical but unproven hypothesis.

The lack of proportionality between delivery and improvement in efficacy may be due to the heterogeneity of asthma severity in the patients included in the trials, the use of improvement in lung function, as measured by FEV_1 , as the primary outcome measure, or possibly, decreased conversion of beclomethasone dipropionate in the lung to its active monopropionate ester due to more rapid systemic absorption of the smaller soluble particles. Evidence for the latter effect comes from studies showing similar decreases in 24-hour UFC excretion produced by the HFA-MDI beclomethasone dipropionate at both one-half and at the same microgram dose of the CFC-MDI.⁴⁷ In addition, plasma AUCs for total beclomethasone were similar for one-half dose HFA-MDI and CFC-MDI and greater for the HFA-MDI at the same microgram dose. Thus, there was greater overall systemic availability of total beclomethasone from the HFA-MDI, as would be expected from the increased lung delivery. In contrast, the flunisolide HFA-MDI preparation delivers approximately 3 times the amount of flunisolide delivered by the CFC-MDI, and comparative clinical trials show that flunisolide HFA-MDI produces clinically comparable results to flunisolide CFC-MDI at one-third the labeled dose.^{48,49}

The newest inhaled corticosteroid, ciclesonide, delivers approximately 50% of the ex-actuator dose to the lungs.⁵⁰ When compared with fluticasone propionate HFA-MDI, beclomethasone dipropionate CFC-MDI, and budesonide DPI, ciclesonide has similar efficacy when accounting for its relative potency (less than fluticasone propionate and greater than budesonide) and difference in delivery (greater than fluticasone propionate HFA-MDI and budesonide DPI).²⁻⁵ Ciclesonide would be expected to provide equal efficacy to fluticasone propionate HFA-MDI in equivalent microgram doses based on its relative potency and delivery, but the formulations of ciclesonide 80 and 160 µg/puff do not match fluticasone propionate HFA-MDI at 44, 110, and 220 µg/puff. Therefore, comparisons at high doses have used 880 and 1760 µg/day of fluticasone propionate versus 1280 µg/day of ciclesonide; these dosing differences are not large enough to detect efficacy differences, but are large enough to show differences in sensitive measures of systemic availability (24-h UFC and serum cortisol AUC₀₋₂₄).⁵¹

Pharmacokinetic Differences

The pharmacokinetic differences for inhaled corticosteroids are what determine their relative topical to systemic effect ratio or therapeutic index. Factors that enhance the therapeutic index are decreased oral absorption, retention in the lung, and rapid systemic clearance once the drug is absorbed into the systemic circulation.⁹⁻¹⁴ More recently, it has been posited that high plasma protein binding would also enhance the therapeutic index.^{2,13,14} Pharmacokinetic differences between the inhaled corticosteroids are listed in Table 2. Because the first CFC-MDI preparations delivered the majority (70–80%) of the drug into the oropharynx, which was then swallowed, decreasing oral bioavailability by either decreased absorption or first-pass metabolism by the gut lining or the liver significantly enhanced the therapeutic index of the first inhaled corticosteroids (beclomethasone dipropionate, flunisolide, triamcinolone acetonide) over the dexamethasone MDI, which was 100% orally available.⁹ Then, budesonide and fluticasone propionate had reduced oral bioavailability that further enhanced their therapeutic indexes, although the difference between beclomethasone dipropionate and budesonide could be overcome with the use of a spacer device that reduced oropharyngeal deposition.^{9,22,33} The 2 newest inhaled corticosteroids (mometasone furoate and ciclesonide) have very low oral bioavailability, similar to that of fluticasone propionate (Table 2).²⁷

Retention of an inhaled corticosteroid in the lung following inhalation can be accomplished by distribution into the lipophilic tissues of the lung and slow absorption into the systemic circulation, resulting in more prolonged apparent elimination half-life following inhaled administration versus intravenous administration.^{9,11} Another possible mechanism for prolonging retention in the lung is intracellular fatty acid es-

terification with inhaled corticosteroids that have a free hydroxyl group at the carbon 21 position (ie, budesonide, triamcinolone acetonide, des-ciclesonide).^{11,14} Although fatty acid esterification can be shown both in vitro and in vivo, this property has not been established to confer an improved therapeutic index or prolonged duration of effect over agents that do not undergo esterification.^{11,14,52}

It has been hypothesized that high plasma protein binding would diminish tissue distribution, thus enhancing the therapeutic index of inhaled corticosteroids; however, available data do not support this hypothesis.^{5,7,8} Mometasone furoate, 1 of the 2 inhaled corticosteroids with the highest protein-binding (Table 2), has not demonstrated an improved therapeutic index over fluticasone propionate, which shares the same pharmacokinetic profile.^{7,53} In addition, the relatively low affinity binding to serum albumin is not restrictive in that the distribution volume and systemic clearance of both mometasone furoate and des-ciclesonide are high.^{2,7}

Systemic clearance and bioavailability are the primary determinants of systemic exposure of a drug. All of the currently available inhaled corticosteroids undergo extensive metabolic conversion in the liver, primarily by the CYP3A4 enzyme subfamily, with unrestrictive hepatic extraction.^{11,14} Systemic clearance of inhaled corticosteroids is primarily limited by hepatic blood flow (~90 L/h). However, des-ciclesonide and beclomethasone monopropionate have clearance exceeding hepatic blood flow, reflecting extrahepatic elimination, possibly via blood esterase activity.^{2,54} The high oral availability of beclomethasone monopropionate (~40%) counteracts the effect of higher clearance on therapeutic index. However, the 2-fold greater clearance of des-ciclesonide, with its concomitant low oral availability, should provide an enhanced therapeutic index. Current data are inconclusive, as studies seldom have used dose-ranging or equivalent doses.^{3,4} One dose-ranging trial noted that 1760 µg/day of fluticasone propionate CFC-MDI produced a significant reduction in 24-hour UFC compared with placebo and that the value for 1280 µg/day of ciclesonide was between that seen for 880 µg/day and 1760 µg/day of fluticasone propionate, as one would predict based on potency and delivery differences.⁵¹ Thus, further studies are needed to assess the therapeutic index of ciclesonide relative to that of other inhaled corticosteroids.

Drug Interactions

An addition to the new dosing tables for inhaled corticosteroids is the warning concerning potentially clinically significant drug interactions with a number of the inhaled corticosteroids and potent inhibitors of CYP3A4 isozymes (eg, ketoconazole, itraconazole, ritonavir).¹ The interaction is most likely due to increased oral bioavailability, as it is affected to a greater extent than systemic elimination for high hepatic extraction drugs and that CYP3A4 isozymes

are in abundance in the intestinal lining, facilitating the high first-pass effect.⁵⁵ Numerous reports of clinically significant Cushing's syndrome and adrenal insufficiency in both children and adults have appeared in the literature secondary to the combination of fluticasone propionate or budesonide with a CYP3A4 inhibitor.⁵⁶⁻⁵⁹ The vast majority of these patients were receiving high doses of the inhaled corticosteroid prior to beginning the inhibitor. Both mometasone furoate and des-ciclesonide plasma concentrations significantly increase with concomitant ketoconazole administration. Flunisolide and beclomethasone dipropionate are also metabolized by CYP3A4. Thus, clinicians should be aware of the need to use lower doses of most inhaled corticosteroids with coadministration of CYP3A4 inhibitors.

Once-Daily Dosing

Mometasone furoate was the first inhaled corticosteroid to obtain FDA-approved labeling for once-daily dosing as a starting dose. Budesonide DPI obtained FDA approval for once-daily dosing for patients who were initially stabilized on twice-daily dosing and budesonide inhalation suspension has been approved for initial once-daily dosing. Beclomethasone dipropionate HFA-MDI, ciclesonide HFA-MDI, flunisolide HFA-MDI, and fluticasone propionate HFA-MDI all have FDA-approved labeling for twice-daily dosing. The initial 2 pivotal trials for ciclesonide HFA-MDI in children 4–11 years old showed that once-daily dosing failed to produce conclusive evidence of efficacy. However, data from the 2 studies were published as an integrative analysis that reported significantly improved lung function over placebo treatment for the 2 higher doses.⁶⁰ The differences were quite small and of questionable clinical significance, with only 2.9% and 3.5% greater improvement shown in mean baseline FEV₁ percent predicted for 80 and 160 µg once daily, respectively. However, a comparison of ciclesonide 80 µg twice daily with fluticasone propionate 88 µg twice daily in children 4–15 years of age with persistent asthma reported that both treatments improved prebronchodilator FEV₁ significantly above baseline and were not significantly different from each other.⁵

It is unclear whether the differences in indications for once-daily versus twice-daily dosing represent real differences between the various inhaled corticosteroids or whether they are solely based on the dosing or entry criteria in the pivotal trials.⁶¹ Most of the inhaled corticosteroids have demonstrated efficacy with once-daily dosing, although they are more effective in patients with more moderate-to-severe asthma when given twice daily.^{2,62-67} Neither budesonide nor mometasone furoate has unique pharmacokinetic properties that would favor once-daily dosing. The pharmacokinetic profile of mometasone furoate is similar to that of fluticasone propionate, only with lower lipophilicity and distribution volumes that

would not favor retention in the lung. Ciclesonide and flunisolide also undergo fatty acid esterification similar to that of budesonide, and des-ciclesonide has a distribution volume similar to that of fluticasone propionate.^{11,14}

Limitations of Studies

The clinical comparative chart is based on comparative efficacy trials and not studies that assess the therapeutic index of the inhaled corticosteroids. Too few studies assess relative therapeutic indexes.¹⁷ Those that do tend to be short term and use surrogate biomarkers as opposed to clinical outcomes.^{3,4,30,31} The dose response to inhaled corticosteroids is relatively flat, making it very difficult to detect dose-response differences between doubling doses.^{18,19,30} The pivotal clinical trials submitted to the FDA to gain approval of the drugs are not designed to determine whether a patient does not respond adequately to a low dose, with dose escalation required to improve control. Instead, each pivotal trial for each dose of the inhaled corticosteroids is run separately, with different entry criteria, so it is unknown whether patients on high doses may have been adequately controlled with low doses or whether patients uncontrolled on low doses would be controlled on high doses. The best studies for assessing dose response of the inhaled corticosteroids have been in those comparing escalating doses of inhaled corticosteroids with the addition of a long-acting inhaled β_2 agonist.^{20,68-70} The studies assessing prevention of exacerbation clearly demonstrate significant reduction in exacerbation when the inhaled corticosteroid dose is quadrupled over the baseline dose.⁶⁸⁻⁷⁰

Summary

Inhaled corticosteroids all share properties that make them effective topical antiinflammatory agents for treatment of asthma with minimal adverse systemic effects, particularly when administered in low- to medium-dose ranges. The EPR3 has provided the clinician with a comparative dosing chart based on comparative clinical trials. While there are differences among the inhaled corticosteroids in pharmacokinetic properties that can improve the therapeutic indexes, this has not yet been adequately assessed in comparative dose-ranging studies to make firm conclusions.

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Comparación de Corticosteroides Inhalados: Una Actualización

HW Kelly

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EXTRACTO

OBJETIVO: Resumir la base del reporte del Panel de Expertos de Instituto Nacional de Corazón, Pulmón, y Sangre donde se incluyen las dosis comparativas estimadas de las dosis diarias de los corticosteroides inhalados (CSI) en niños y adultos. Además se discute la base farmacocinética y farmacodinámica las potenciales diferencias clínicas entre los CSIs.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda completa para identificar estudios clínicos en MEDLINE sobre la farmacoterapia de asma de enero 1, 2001 a marzo 15, 2006, seguida por una búsqueda en PubMed hasta agosto 2008 utilizando como términos ciclesonide, corticosteroides inhalados y farmacocinética. Se utilizó además la información de producto de cada CSI.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE LA INFORMACIÓN: Se utilizaron estudios clínicos comparativos de CSIs y resúmenes sistemáticos para comparar eficacia. Se seleccionaron resúmenes extensos de literatura, meta-análisis estudios clínicos que ilustraran o presentaran puntos de vista específicos. Además se extrajo data farmacodinámica y farmacocinética de resúmenes publicados y de estudios específicos.

SÍNTESIS: Las características farmacodinámicas (enlace al receptor de glucocorticoide) y la liberación al pulmón determina la eficacia clínica relativa y las propiedades farmacocinéticas (biodisponibilidad oral, retención del pulmón, y aclaración sistémica) determinan el índice terapéutico comparativo de los CSIs. Las diferencias farmacocinéticas secundarias (esterificación de ácido graso y el alto enlace a proteína sérica) que han sido posicionadas para mejorar la duración de acción y/o el índice terapéutico no han sido probados y los estudios clínicos comparativos actuales no apoyan el que estos ofrezcan alguna ventaja. Los inhaladores de dosis premedida con partículas ultra finas no han demostrado un control de asma superior ni mejor perfil de seguridad sobre los antiguos inhaladores de dosis premedida antiguos. Todos los CSIs demuestran eficacia con una dosis diaria. Y todos son más efectivos al administrarse 2 veces al día.

CONCLUSIONES: La evidencia actual sugiere que todos los CSIs tienen un índice terapéutico adecuado para proveer una eficacia y seguridad similar al

administrarse dosis de bajas a medianas. Si algunos de los nuevos CSIs ofrece o no alguna ventaja en dosis altas todavía esta por determinarse.

Traducido por Annette Pérez

Mise à Jour sur la Comparaison des Corticostéroïdes en Inhalation

HW Kelly

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RÉSUMÉ

OBJECTIFS: Revoir les données ayant servi au National Heart, Lung, and Blood Institute's Expert Panel 3 à l'estimation des doses quotidiennes comparatives des corticostéroïdes en inhalation (CSI) chez les enfants et les adultes. De plus, les données sur la pharmacodynamie et la pharmacocinétique pouvant expliquer les différences cliniques sont discutées.

SOURCES DES DONNÉES: Une recherche dans MEDLINE portant sur les études humaines de pharmacothérapie de l'asthme publiées entre le premier janvier 2001 et le 15 mars 2006, suivie d'une recherche dans PubMed jusqu'en août 2008 en utilisant les mots-clés ciclesonide, inhaled corticosteroids et pharmacokinetics. Les monographies de chacun des ICS ont également été révisées.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Les essais cliniques comparatifs et les revues systématiques comparant l'efficacité ont été retenus, de même que les revues de littérature, les méta-analyses et des essais cliniques qui illustraient des points de vue spécifiques. Les données de pharmacodynamie et de pharmacocinétique ont été extraites de publications antérieures.

SYNTHÈSE DES DONNÉES: Les caractéristiques pharmacodynamiques (liaison au récepteur) et la disponibilité dans les poumons déterminent l'efficacité clinique relative et la pharmacocinétique (biodisponibilité orale, rétention pulmonaire, et clairance systémique) déterminent les index thérapeutiques. Les différences secondaires de pharmacocinétique (estérification des acides gras dans les cellules et une liaison aux protéines élevée) ayant été associées à une amélioration de la durée d'action ou à un index thérapeutique demeurent non fondées et les essais cliniques ne permettent pas de conclure à un avantage thérapeutique. Les inhalateurs de particules très fines n'ont pas été associés à un meilleur contrôle de l'asthme ni à une meilleure innocuité que les inhalateurs traditionnels. Tous les CSI ont démontré une efficacité avec une administration par jour et sont plus efficaces lorsqu'administrés 2 fois par jour.

CONCLUSIONS: Les données actuelles suggèrent que tous les CSI ont des index thérapeutiques suffisants pour offrir une efficacité et innocuité comparables avec des doses faibles à modérées. Les avantages des nouveaux CSI à des doses élevées restent encore à être démontrés.

Traduit par Nicolas Paquette-Lamontagne