Comparing Inhaled Corticosteroids

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Introduction

At present in the United States, there are 5 different corticosteroids available for use via the inhalation route (Table 1). These are beclomethasone dipropionate (BDP), budesonide, flunisolide, fluticasone propionate, and triamcinolone acetonide. Extensive information has been compiled on the differences in pharmacologic profiles among these products. Both in vivo and in vitro testing suggests that these 5 inhaled corticosteroids may have clinically relevant differences in potency. Consequently, asthma management guidelines indicate that equal doses of these products should not be expected to have equivalent clinical effects.[1] Dosing regimens must be adjusted for the severity of asthma when switching from use of one inhaled corticosteroid to another (Table 2).

Another important distinguishing feature among these products is the delivery device used for inhalation administration. Three of these inhaled corticosteroids (BDP, flunisolide, and triamcinolone acetonide) are marketed in metered-dose inhalers (MDIs), one (budesonide) is available only in a dry powder inhaler (DPI), and one (fluticasone propionate) is available in both an MDI and a DPI form. The inhaled corticosteroids currently available in MDIs are formulated in the traditional chlorfluorocarbon (CFC) propellants. The United States Food and Drug Administration (FDA) is currently reviewing new drug applications for several inhaled corticosteroids reformulated in non-CFC propellants (BDP, fluticasone, and triamcinolone acetonide). A new drug application has been submitted to the FDA for an inhaled corticosteroid (fluticasone) reformulated in a new type of DPI. In addition, a novel inhaled corticosteroid (mometasone furoate) formulated in a DPI is also being evaluated by the FDA.

As a result of these pharmaceutical development efforts, conceivably within the near future, respiratory clinicians will have 6 different inhaled corticosteroids in various inhalation delivery devices available for use. Comparing these inhaled corticosteroids will be an important concern for health care professionals in choosing the most appropriate treatment for patients with respiratory disease.

Therapeutic Indications for Inhaled Corticosteroids

In the United States, the only currently approved indication for inhaled corticosteroids is as prophylactic therapy for the maintenance treatment of asthma. There has been considerable interest in using inhaled corticosteroids for other diseases, most notably chronic obstructive pulmonary disease and sarcoidosis. Clinical data obtained from large trials show that the use of inhaled corticosteroids in chronic obstructive pulmonary disease may confer small advantages in preserving lung function[2] and reducing ex-

Table 1. Currently Approved Inhaled Corticosteroids

Generic name	Beclomethasone Dipropionate	Budesonide	Flunisolide	Fluticasone Propionate	Fluticasone Propionate	Triamcinolone Acetonide
Brand name (manufacturer)	Beclovent (Glaxo Wellcome) Vanceril and Vanceril DS (Schering Plough)	Pulmicort Turbuhaler (Astra Zeneca)	Aerobid and Aerobid-M (Forest)	Flovent (Glaxo Wellcome)	Flovent Rotadisk (Glaxo Wellcome)	Azmacort (Rhône-Poulenc Rorer)
Dosage form	MDI 42 μg/puff ex-actuator (84 μg/puff for the double-strength product)	DPI 200 μg/dose	MDI 250 μg/puff ex-actuator	MDI 44, 110, or 220 μg/puff ex-actuator	DPI 50, 100, or 250 μg/dose	MDI with built-in spacer 100 μg/puff ex-spacer
Recommended adult daily dose	252–840 μg 2 puffs tid–10 puffs bid (half the number of puffs for the double-strength product)	400–1,600 μg 1 dose bid–4 doses bid (stable patients can be maintained on 1 dose of 200 μg/d)	1,000–2,000 μg 2 puffs bid–4 puffs bid	176–1,760 μg 2 puffs bid (44)–4 puffs bid (220)	200–2,000 μg 2 doses bid (50)–4 doses bid (250)	600–1,600 μg 2 puffs tid–8 puffs bid
Recommended pediatric daily dose	Age 6–12 132–420 μg 1 puff tid–5 puffs bid	Age 6–12 400–800 μg 1 dose bid–2 doses bid (stable patients can be maintained on 1 dose of 200 μg/d)	Age 6–15 1,000 μg 2 puffs bid	Not approved for this age group	Age 4–11 100–200 μg 1 dose bid (50)–2 doses bid (50)	Age 6–12 300–1,200 μg 1 puff tid–6 puffs bid

MDI = metered-dose inhaler. DPI = dry powder inhaler.

Table 2. Doses of Inhaled Corticosteroids Recommended by the National Asthma Education and Prevention Program for Adults by Severity of Asthma*

	Beclomethasone Dipropionate	Budesonide	Flunisolide	Fluticasone Propionate (MDI)	Fluticasone Propionate (DPI)	Triamcinolone Acetonide
Low dose for mild, persistent	168–504 μg/d	200–400 μg/d	500–1,000 μg/d	88–264 μg/d	100–300 μg/d	400–1,000 μg/d
Medium dose for moderate, persistent	504–840 μg/d	400–600 μg/d	1,000–2,000 μg/d	264–660 μg/d	300–600 μg/d	1,000–2,000 μg/d
High dose for severe, persistent	> 840 μg/d	> 600 μg/d	> 2,000 μg/d	> 660 μg/d	> 600 μg/d	> 2,000 μg/d

*These recommendations are taken from the Expert Panel II report[1] and do not necessarily conform to FDA-approved dosing.[1]
MDI = metered-dose inhaler. DPI = dry powder inhaler.

acerbation rates.[3] However, it is unclear whether these benefits warrant the cost, inconvenience, and potential risks of long-term treatment of chronic obstructive pulmonary disease with inhaled corticosteroids. Although preliminary data suggested that inhaled corticosteroids might be effective in the treatment of sarcoidosis,[4] recent work has not been able to confirm this benefit.[5]

By United States and international guidelines on asthma management,[1,6] inhaled corticosteroids are accepted to be the most useful medication currently available for the con-

trol of persistent asthma symptoms. The beneficial effects of inhaled corticosteroids in asthma relate to the basic pathophysiology of this disease and the known pharmacologic effects of this class of drugs. Asthma is a disease clinically recognized by airway hyperresponsiveness, but it is really an inflammatory airway disease. The inflammation extends from the large airways to the small airways.[7,8] Airway inflammation can be found at the first presentation of patients with asthma symptoms,[9] and is evident even in patients with mild, intermittent symptoms.[10]

A characteristic histologic feature of inflammation in asthma is infiltration of airway walls by eosinophils. A more recently recognized feature of inflammation in asthma is remodeling of airway walls, specifically, thickening of the lamina reticularis just below the basement membrane of the airway epithelium.[11] Airway remodeling may contribute to chronic air flow obstruction in asthma.

Corticosteroids have direct inhibitory effects on several of the inflammatory cells implicated in the pathogenesis of asthma.[12] These drugs reduce the number of circulating eosinophils, by either a direct action at the bone marrow level or through reducing the levels of cytokines known to be required for eosinophil survival. Mucosal mast cell numbers also decrease with corticosteroid treatment, again possibly because of reduction in the cytokines and growth factors necessary for mast cell survival. Corticosteroids directly inhibit release of inflammation mediators from lymphocytes, alveolar macrophages, and airway epithelial cells. In addition, corticosteroids are known to reduce mucus secretion in airways, possibly by a direct inhibitory effect on submucosal gland cells.

The molecular mechanisms by which corticosteroids exert their anti-inflammatory effects are not entirely understood. Corticosteroids are known to bind with cytoplasmic receptors. The corticosteroid-receptor complexes translocate to the nucleus, bind to recognition sequences on corticosteroid responsive genes, and directly affect transcription of genomic content. However, the anti-inflammatory effects of corticosteroids probably cannot be explained entirely by their interactions with corticosteroid response genes. Corticosteroids were recently found to interact with other cytoplasmic factors, such as activator protein-1 and nuclear factor-κB, which also affect genomic transcription. It is becoming more apparent that corticosteroids have a complex effect on intracellular function. Whether the cumulative effects of corticosteroids on genetic transcription are an increase in cellular anti-inflammatory protein synthesis, a decrease in inflammatory protein synthesis, or a combination of both is not clear.

In clinical practice, inhaled corticosteroids effectively reduce airway inflammation in asthma patients. Improvements in lung function and reduction of asthma symptoms with the use of inhaled corticosteroids have been directly related to a decrease in airway inflammation.[13] The long-term use of inhaled corticosteroids has been shown to reduce both airway inflammation and secondary airway remodeling.[14] The fundamentally important role of inhaled corticosteroids in treating asthma has been demonstrated by several studies, which showed that the maximum beneficial effect is achieved with early use of these drugs. For example, delaying use by relying on bronchodilators alone to manage symptoms reduces the improvement in lung function potentially achievable with inhaled corticosteroids.[15,16]

In the treatment of asthma, corticosteroids may be administered in a variety of ways other than the inhaled route, including orally or systemically as either an intravenous or intramuscular injection. In severe cases of asthma, oral or systemic administration of corticosteroids is preferred. However, potentially serious disadvantages of oral and systemic administration of corticosteroids include the risk of systemic adverse effects. With prolonged use of oral and systemic corticosteroids comes the risk of suppression of the hypothalamic-pituitary adrenal axis, inhibition of growth in pediatric patients, and osteoporosis in adults, skin thinning, easy bruisability, ocular cataracts, abnormalities in carbohydrate and lipid metabolism, change in body habitus, and mood disorders. An important advantage of inhaled corticosteroids is that they have been shown to have a topical anti-inflammatory effect.[17] Consequently, inhaled corticosteroids achieve and maintain beneficial anti-inflammatory effects with much lower total daily doses and much less risk of serious adverse effects than oral or systemic corticosteroids.

Methods for Comparing Inhaled Corticosteroids

Potency

The term "potency" refers to the strength of the physiologic or pharmacologic response to a known concentration of a drug. Although potency implies a bearing on clinical efficacy, this may not always be the case. The actual relationship between potency and clinical efficacy is complex, because the physiologic or pharmacologic test used in assessing potency may not accurately reflect the disease pathophysiology. Inhaled corticosteroids provide a good example of the difficulties encountered in relating potency to clinical efficacy. The most commonly used test to assess the potency of inhaled corticosteroids is the MacKenzie skin blanching test. The corticosteroid to be tested is formulated in a solution and placed on the skin for several hours. The degree of blanching or whitening of the underlying skin is used as the measure of potency. However, skin blanching reflects vasoconstriction, which is not a prominent feature of asthma pathophysiology. Furthermore, the vascular structure of the skin is substantially different than that of the lung. Relative potencies of the 5 currently available inhaled corticosteroids have been measured using the MacKenzie skin blanching test (Table 3), but should only be interpreted in the context of clinical trial results.[18]

Other methods for estimating potency of inhaled corticosteroids involve measuring the receptor binding affinity and the receptor binding half-life. A drug that binds more avidly to receptors for longer time periods might be expected to be more effective. There are limitations to these tests, however. The cells used for in vitro testing of re-

Table 3. Relative Topical Potencies and Receptor Binding Characteristics of Currently Available Inhaled Corticosteroids

	Beclomethasone Dipropionate	Budesonide	Flunisolide	Fluticasone Propionate	Triamcinolone Acetonide
MacKenzie skin blanching test*	600	980	330	1,200	390
Receptor binding affinity*	0.4	9.4	1.8	18.0	3.6
Receptor binding half-life (hours)	Not known	5.1	3.5	10.5	3.9

*Relative to dexamethasone with a value of 1.

ceptor binding affinity and receptor binding half-life might not accurately reflect the binding affinities of relevant inflammatory cells such as eosinophils and mast cells. A more fundamental difficulty with this approach is apparent from the emerging view of the molecular mode of action of corticosteroids. It is becoming clear that corticosteroids are interacting with cells in more complex ways than can be accounted for by receptor binding alone, as discussed above. Accepting these difficulties with relating binding affinity and half-life to cellular effects, the known binding characteristics of inhaled corticosteroids (see Table 3) should be interpreted cautiously.[18]

More recently, attempts have been made to relate in vitro corticosteroid receptor binding affinity to transcriptional activity of genes known to be controlled by the corticosteroid receptor.[19] As the genes responsible for the anti-inflammatory effects of corticosteroids become better understood, this approach may be very useful in relating in vitro measures of potency to clinical measures of efficacy. Another approach to comparing the potency of inhaled corticosteroids is to measure histamine release from basophils, eosinophil viability, and eicosanoid release from airway epithelial cells after prolonged culture with the various drugs.[20,21] The advantage to this approach is the use of cells accepted to be intimately related to the pathogenesis of asthma.

Pharmacokinetics/Pharmacodynamics

The usual approaches to assessing the pharmacokinetic profile of a drug rely on measuring serum concentrations over time and calculating such factors as peak serum concentration, time to peak serum concentration, serum half-life, and integrated serum concentration over time (also known as the area-under-the-curve of serum concentration). Unfortunately, these standard pharmacokinetic assessments provide little insight into differences among inhaled corticosteroids, because the efficacy of these drugs is related to their topical anti-inflammatory effects and not their serum concentrations. For inhaled corticosteroids, their pharmacodynamic profile, which is the relationship between drug dose and drug effect, relates to the intrapul-

monary handling of the inhaled drug. Recent work indicates that for some inhaled corticosteroids there is a dissociation between serum concentration of the drug and concentration in lung tissue. Fluticasone propionate has been shown to be retained in lung tissue for much longer than is evident from serum concentrations.[22] The implication of this finding is that the topical anti-inflammatory effect will persist for much longer than the risk of systemic adverse effects.

Because it is difficult to estimate topical airway anti-inflammatory effects from serum concentrations of an inhaled corticosteroid, an alternative method for comparing inhaled corticosteroids has been proposed. This approach is based on calculating the lung and systemic biovailability profiles of the various products. The bioavailability of a product relates the integrated serum concentration of a drug over time to the dose administered. Bioavailability of a product depends on the method of administration. Intravenous administration is typically used to measure systemic bioavailability and is an accepted reference standard for drugs administered via inhalation. Relating bioavailability after inhalation delivery to systemic bioavailability allows calculation of lung bioavailability. High lung bioavailability relative to systemic bioavailability indicates that more of the drug reached the systemic circulation via the lungs, and, consequently, provided beneficial topical anti-inflammatory effects.

Estimating the lung-to-systemic bioavailability ratio provides a basis for understanding the therapeutic index of an inhaled corticosteroid. The therapeutic index quantifies the relationship between benefits and risks of administering any drug. The concept of relative therapeutic indices is probably most easily understood by comparing the use of inhaled corticosteroids and oral/systemic corticosteroids in asthma. The beneficial effect of administering corticosteroids by any route is the anti-inflammatory effect. However, the benefits of an inhaled corticosteroid in treatment of asthma are clearly the topical anti-inflammatory effects. In other words, by administering the drug directly to the airways (the site of inflammation) the dose can be kept sufficiently low that systemic anti-inflammatory effects (and, presumably, systemic adverse effects) are avoided. Oral and systemic corticosteroids reach

the lung secondarily through the systemic circulation and cause both systemic and local (respiratory tract) anti-inflammatory effects. However, the risks of systemic adverse effects is, obviously, much greater, because the corticosteroid reaches the systemic circulation through nonpulmonary routes, either the gastrointestinal tract or the venous system. In general, inhaled corticosteroids have a more favorable therapeutic index than oral or systemic corticosteroids because the beneficial anti-inflammatory effects are achieved with much less risk of systemic adverse effects. Conceptually, inhaled corticosteroids can be viewed as having a high lung bioavailability and a low systemic bioavailability (ie, the products are delivered directly to the lung and little gets into the systemic circulation). Oral and systemic corticosteroids have a relatively low lung bioavailability (only a portion reaches the lungs and most is distributed throughout the rest of the body) but a high systemic bioavailability.

The therapeutic index of various inhaled corticosteroids can be compared in a similar way. Products with the most favorable therapeutic index have most of the drug entering the body through the lungs (ie, high lung bioavailability) and only a small amount reaching the systemic circulation through nonpulmonary routes (ie, low systemic bioavailability). This type of comparison is possible because the pharmaceutical industry has developed inhaled corticosteroids that differ substantially in their lung deposition and metabolic characteristics. For the inhaled corticosteroids that have been commercially available for more than 5–10 years, only a small percentage of the drug released from the delivery device actually reaches the lower respiratory tract.[23] Most of the aerosolized particles released from the delivery device and carrying drug actually impact on the tongue or the posterior oropharynx. These particles are subsequently swallowed; swallowed drug may eventually reach the systemic circulation after being absorbed in the gastrointestinal tract and passing through the hepatic circulation. The therapeutic index is still favorable compared to oral and systemic corticosteroids, but is not ideal, because drug reaching the systemic circulation through the gastrointestinal tract may cause systemic adverse effects

with minimal contribution of airway anti-inflammatory benefit.

Recognizing the historic limitations of delivering inhaled corticosteroids to the airways, the pharmaceutical industry took two different approaches to improve the therapeutic index of these products. The first approach was to increase the metabolism of absorbed drug by the liver so that, even though the drug might have poor lung deposition characteristics, any swallowed drug would be broken down in the liver and thus unlikely to reach the systemic circulation. Another approach was to improve the lung deposition characteristics of the inhaled corticosteroid. The inhaled corticosteroid currently available with the best lung deposition profile is budesonide, but even with this product only about 25–30% of the aerosolized drug reaches the lungs. A newer product, though, has much improved lung deposition characteristics: approximately 55–60% of the ex-actuator dose of BDP formulated in a non-CFC propellant reaches the lower respiratory tract.[24] The majority of drug with excellent lung deposition characteristics that reaches the systemic circulation has passed through the lungs and provided topical anti-inflammatory benefits.

An estimate of the lung-to-systemic bioavailability ratio is a surrogate estimate of the therapeutic index of an inhaled corticosteroid. The greater the proportion of drug reaching the systemic circulation through the lungs (lung bioavailability) relative to total systemic bioavailability of drug, the greater the topical anti-inflammatory benefits relative to the risks of systemic adverse effects. Estimates of the lung-to-systemic bioavailability ratio suggest that inhaled corticosteroids that are either metabolized extensively by the liver (such as fluticasone) or have excellent lung deposition characteristics (such as the new BDP product) will be preferred (Table 4).

Clinical Trials

Inherent in our understanding that inhaled corticosteroids provide their benefits through topical anti-inflammatory effects is an appreciation that surrogate measures such

Table 4. Estimates of the Lung to Systemic Bioavailability Ratios for Inhaled Corticosteroids*

Product	% Dose Deposited in the Lungs	% Dose Reaching the Systemic Circulation after Absorption from the Gastrointestinal Tract	Lung/Systemic Bioavailability Ratio
BDP via CFC propellant	5.5	14.7	0.27
BDP via non-CFC propellant	56.1	5.5	0.92
Budesonide via MDI	15	7.7	0.66
Budesonide via DPI	30	5.3	0.85
Fluticasone propionate via DPI	12	0.6	0.95

*Data from personal communication with 3M Pharmaceuticals, St Paul, Minnesota, 1999.
BDP = beclomethasone dipropionate. CFC = chlorofluorocarbon. MDI = metered-dose inhaler. DPI = dry powder inhaler.
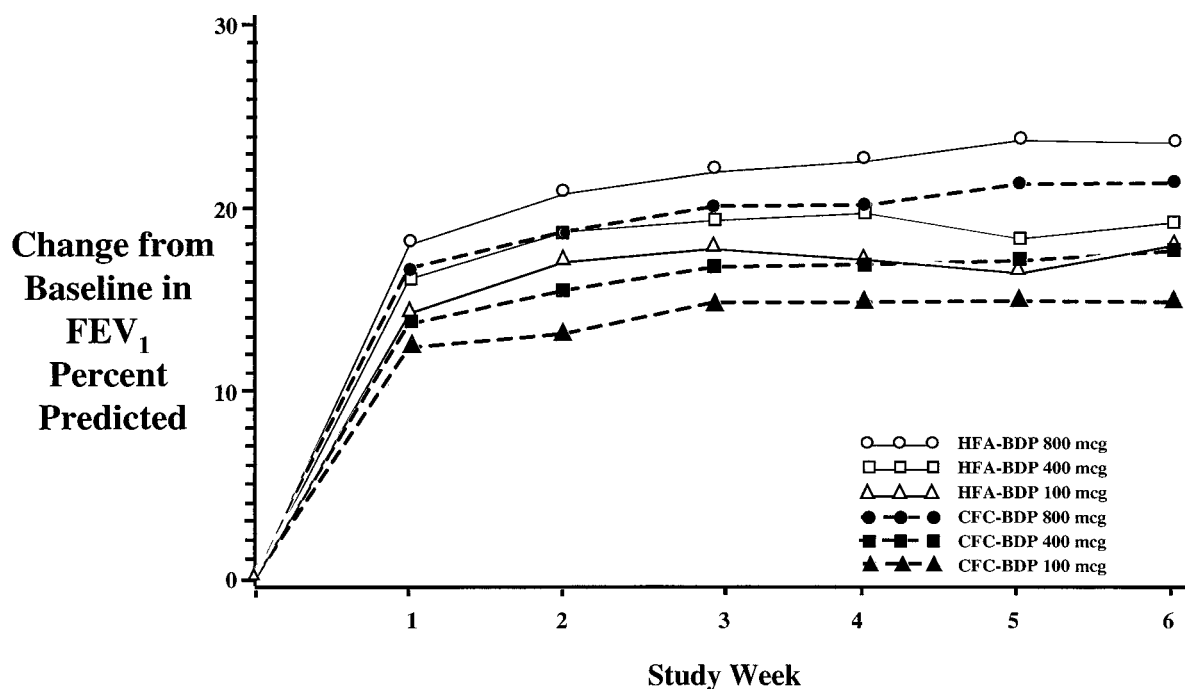
Fig. 1. The change from baseline in forced expiratory volume in the first second (FEV_1) percent of predicted is shown for the study comparing beclomethasone dipropionate (BDP) formulated in chlorofluorocarbon (CFC) propellant (filled circles, squares, and triangles) with BDP formulated in a non-CFC propellant (hydrofluoroalkane [HFA]) (open circles, squares, and triangles) over the 6 weeks of the study. Three different doses of each product were used. Note that there was increasing benefit for each product as dose was increased. Also, at each dosing level there was greater benefit from the non-CFC BDP product. (Adapted from Reference 25.)

as potency and estimates of lung and systemic bioavailability will not be true measures of the differences among inhaled corticosteroids. The most useful and clinically relevant method for comparing inhaled corticosteroids should be based on patient trials. However, historically, the use of clinical trials to compare inhaled corticosteroids has not been successful,[12] because of a combination of factors, particularly related to two features of study design. To compare inhaled corticosteroids, it is first essential to include patients who are known to be responsive to inhaled corticosteroids. It is also critical to include multiple doses of the inhaled corticosteroids being compared to demonstrate dose response (ie, increasing effect with increasing dose). Only by demonstrating a dose response can the effects of two different inhaled corticosteroids be compared.

A recent study demonstrated that with the proper study design the clinical efficacy of two different inhaled corticosteroids can be distinguished. The study compared the currently available BDP product formulated in CFC propellant with a BDP product formulated in a non-CFC propellant. It was hypothesized that the BDP in the non-CFC propellant would have greater clinical efficacy because it had better lung deposition characteristics. The study design required that asthma patients using inhaled corticosteroids undergo an inhaled corticosteroid washout phase.

Only patients who had a decrease in lung function and an increase in asthma symptoms with inhaled corticosteroid washout were entered into the study. This requirement ensured that the study population was clearly responsive to inhaled corticosteroids. The study design also included 3 different doses of each of the 2 products. The statistical analysis required that increasing benefit be found with increasing doses of each product before the two products could be compared. The results demonstrated (Fig. 1) that this approach was successful in showing that the BDP product formulated in the non-CFC propellant (with better lung deposition characteristics) was indeed more effective in improving lung function and controlling asthma symptoms.[25] This improvement in clinical effect was achieved without compromising systemic safety.[26]

Effects of Inhalation Delivery Device

There has been tremendous interest, both within the pharmaceutical industry and academia, in the development of new types of inhalation delivery devices. At present there are two basic types of inhalation delivery devices commercially available for use with inhaled corticosteroids in the United States: the MDI and the DPI. There are important differences between the two types of DPIs currently available in the United States. The differences be-

tween MDIs and DPIs are further compounded by the common recommendation to use spacer devices with MDIs but not with DPIs. Also, there is considerable variability in pharmaceutic profile (ie, the medication delivery and the medication particle size distribution) among the various inhalation delivery devices. Little research is currently available on the implications of these differences on clinical efficacy; most studies concentrate on the risk of systemic adverse effects with use of different inhalation delivery devices and provide no information on any potential benefits.[27]

One particularly unfortunate aspect of the development of new inhalation delivery devices has been a marketing emphasis on the ease of use of these products, with little data on how this might affect actual patient use. The implication that an easier-to-use product might improve patient adherence with regular use of their inhaled corticosteroids must be substantiated by clinical trial data. Consequently, it is premature to compare either different inhaled corticosteroids or the same inhaled corticosteroid on the basis of type of inhalation delivery device. Fortunately, the respiratory care practicioner can choose among a variety of inhalation delivery devices, based on a needs assessment of the individual patient for the administration of inhaled corticosteroids.

Summary

There are currently available 5 different inhaled corticosteroids, in a variety of different inhalation delivery devices. In the near future there will certainly be more inhaled corticosteroids in newer inhalation delivery devices available in the United States. Tremendous amounts of information will be made available about the relative advantages and disadvantages of these new products. Most of this information will relate to measures of potency, pharmacokinetic profiles, and technical issues about the ease of use. The respiratory care practitioner should be aware that estimating the clinical benefits from the topical anti-inflammatory effects of these newer products will be difficult to determine from this information. Also difficult to understand will be the effects of easier to use inhalation delivery devices on patient adherence to prescribed inhaled corticosteroid dosing regimens. Information from well designed clinical trials should be the basis for comparing presently available and newly developed inhaled corticosteroids.

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