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Inhaled corticosteroids: Past lessons and future issues

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Inhaled corticosteroids play a pivotal role in the treatment of asthma. Inhalation permits effective delivery of the corticosteroid in high concentration to target sites within the lung while minimizing systemic exposure. Consequently, the safety profile of inhaled corticosteroids is markedly better than that of oral corticosteroid therapy. However, although it was first thought that direct delivery might eliminate systemic adverse effects, this has not been confirmed by clinical trials and experience. Inhaled corticosteroids are absorbed from the lungs into the systemic circulation, in which they can acutely decrease growth velocity in children, an effect that fortunately appears to be temporary and might have no effect on final adult height. In sufficient dosages, they also produce bone mineral loss leading to osteoporosis and might increase the risk of cataracts, glaucoma, skin atrophy, and vascular changes that increase the risk of ecchymoses. Effective evaluation of the severity and significance of these complications is challenging because highly sensitive tests do not reliably predict clinically significant events, and short-term observations do not predict long-term consequences. Also, compliance wanes with long-term treatment, and susceptibility to a particular adverse event can vary over time, even in the same individual, because of developmental or hormonal changes. This journal supplement will review

what has been learned about the safety of inhaled corticosteroids during the past decade, discussing some of the questions that remain and considering the characteristics of an “ideal” inhaled corticosteroid: one with high local activity in the lung and minimal or no adverse systemic effects. (*J Allergy Clin Immunol* 2003;112:S1-40.)

Key words: Asthma, cataract, corticosteroids, ecchymosis, glaucoma, glucocorticoids, growth, osteoporosis, skin atrophy

Approximately 5% to 6% of the US population have asthma, a chronic inflammatory disease of the airways.^{1,2} During the past several decades, this prevalence has been increasing by 5% to 6% per year.²⁻⁴

Asthma is costly, resulting each year in 100 million days of restricted activity and 470,000 hospitalizations,¹ with a total economic cost estimated at \$11.3 billion in the United States in 1998.² In addition, asthma causes more than 5000 deaths annually.¹

A better understanding of the pathophysiology of asthma has resulted in improved medical management of this condition.¹ Even in patients who are asymptomatic most of the time, significant airway disease is frequently present,⁵ potentially leading to pathologic remodeling.^{1,5} This understanding has led to guidelines emphasizing the pivotal role of anti-inflammatory inhaled corticosteroids as first-line therapy for patients with asthma.^{1,6} Regular use of low-dose inhaled corticosteroids has been shown to decrease the risk of death, with the degree of risk reduction directly correlated to the amount of inhaled corticosteroid used.⁷

Currently, 5 inhaled corticosteroids—beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, and triamcinolone acetonide—are available to treat asthma in the United States.¹ In addition, several new inhaled corticosteroids (eg, mometasone furoate and ciclesonide) are currently being evaluated. It is important to realize that these agents are not equivalent; significant

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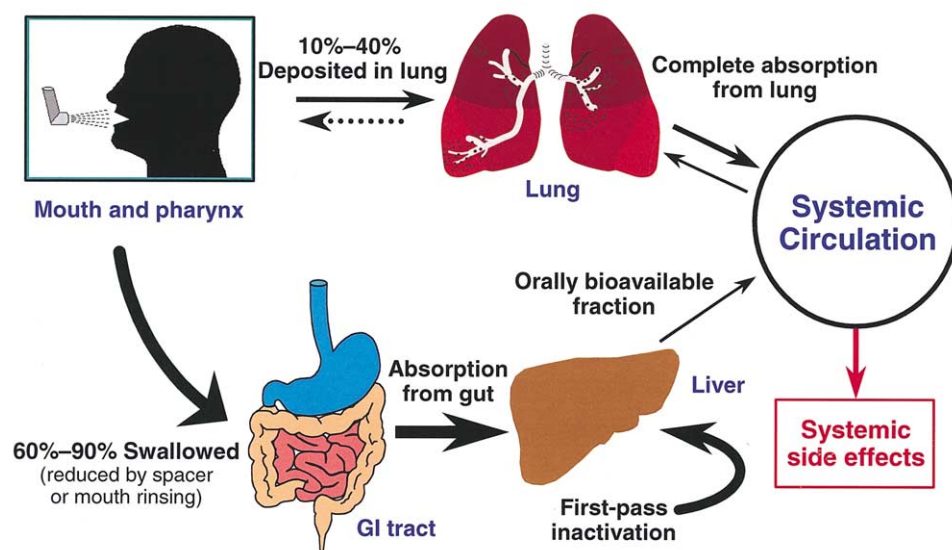


FIG 1. The fate of inhaled corticosteroids.⁸

Abbreviations used

ACRN:	Asthma Clinical Research Network
CAMP:	The Childhood Asthma Management Program
DEXA:	Dual-energy x-ray absorptiometry
DHEA-S:	Dehydroepiandrosterone sulfate
GnRH:	Gonadotropin-releasing hormone
HPA axis:	Hypothalamic-pituitary-adrenal axis
HRD:	Highest recommended dose
LH:	Luteinizing hormone

differences exist that can affect both their efficacy and their safety. This article will consider the necessary properties of an ideal inhaled corticosteroid for use in the treatment of asthma, review what has been learned during the past 10 years about the safety of inhaled corticosteroids, and consider what questions will need to be addressed during the next 10 years.

THE "IDEAL" INHALED CORTICOSTEROID

Fate of inhaled corticosteroids

A determination of what constitutes the ideal inhaled corticosteroid depends on a thorough understanding of the fate of inhaled corticosteroids (Fig 1).⁸ Inhaled corticosteroids use topical delivery to transmit the drug directly to the site of action while limiting systemic exposure; in this way, therapeutic efficacy is maximized and systemic adverse events are minimized. However, a situation that seems relatively simple is actually more complex than it appears. Only a fraction of the dose, approximately 10% to 40% depending on the delivery device, is deposited in the lungs; the rest is swallowed. This swallowed corticosteroid enters the gastrointestinal tract in which, during a prolonged period, it can have

undesired local effects. In addition, the swallowed corticosteroid is itself absorbed from the gastrointestinal tract. Fortunately, most of the swallowed dose undergoes first-pass inactivation in the liver, and only a small portion of it, the orally bioavailable fraction, makes it into the systemic circulation. Part of this orally bioavailable fraction ultimately reaches the lung, in which it has the same effect as the corticosteroid that was topically deposited there. Meanwhile, the topically deposited corticosteroid eventually appears in the systemic circulation. This pathway from the gastrointestinal tract to the systemic circulation and ultimately to the lung is how orally administered corticosteroids work.

Corticosteroid receptors are intracellular. To be efficacious, an inhaled corticosteroid must be able to diffuse across cell membranes to get from the airway into the cytosol; once the corticosteroid enters the cytosol, it ultimately diffuses into the systemic circulation. There is no "magic bullet"; any corticosteroid that works in the lung will eventually enter the systemic circulation.

On the basis of what we now know, it appears that the same receptor type mediates both the beneficial and the adverse effects of corticosteroids. Thus, it is impossible to design a drug that will interact only with receptors having an antiasthma effect. Any drug that interacts with receptors beneficial to the patient also has the potential to interact with receptors that produce adverse events. This is an important concept, because adverse events currently are the limiting factor in the use of corticosteroids; what can be done with these medications will be limited by the adverse events they produce. Therefore, in the treatment of patients with asthma, an ideal inhaled corticosteroid would maximize the amount of active drug present at receptors in the lung while minimizing delivery of the drug to other systemic, adverse event-producing receptors.

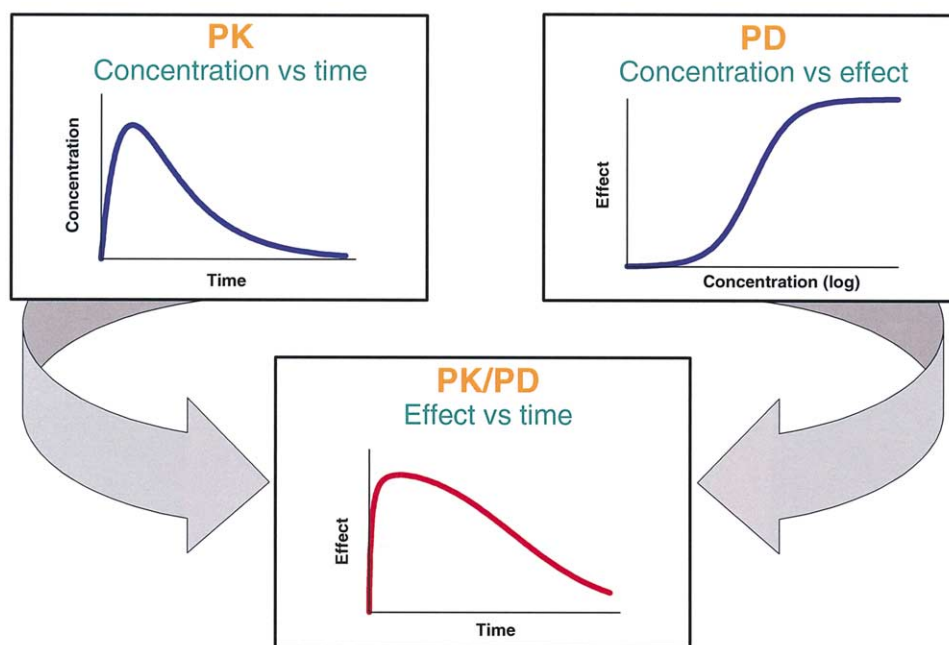


FIG 2. The interrelationship between pharmacokinetics (PK) and pharmacodynamics (PD) in determining the effect of a drug over time. Adapted from Derendorf and Meibohm⁹ and used with permission.

Prodrugs

As will subsequently be discussed, administering an inhaled corticosteroid in the form of a prodrug might be beneficial. Of the 5 currently available inhaled corticosteroids, beclomethasone dipropionate is the only prodrug. Inactive in its native form, it requires metabolism to beclomethasone-17-monopropionate before acquiring activity. However, once activated, beclomethasone-17-monopropionate has one of the highest receptor affinities of any corticosteroid, approximately 13.5-fold greater than that of dexamethasone, the standard for measuring corticosteroid activity. Of note, beclomethasone-17-monopropionate is further metabolized to another active drug, beclomethasone, which has approximately the same receptor affinity as dexamethasone. This metabolism to a second active compound, however, might be a detrimental property of beclomethasone dipropionate; for systemic adverse events to be minimized, a corticosteroid should be metabolized rapidly to inactive products once it leaves the lung and enters the systemic circulation.

Ciclesonide, 1 of the 2 new compounds being evaluated, is also a prodrug that requires activation before it can interact with the receptor.

Pharmacokinetics and pharmacodynamics of corticosteroids

The activity of a drug depends on both its pharmacokinetics and its pharmacodynamics. The pharmacokinetics of a drug determines the concentration-time relationship at the site of action; the pharmacodynamics of the drug determines the relationship between the drug's con-

centration and its clinical effect. The combination of these 2 parameters is necessary to determine the overall effect of the drug over time (Fig 2).⁹ However, unlike drugs such as β -agonists, which have a readily measurable clinical effect, the clinically observed effect of corticosteroids is an anti-inflammatory response that results from receptor occupancy over time. Thus, clinical effect might not be detectable for weeks. Because measurable response to corticosteroids is delayed, the relationship between pharmacokinetics, pharmacodynamics, and drug effect is not as obvious as with other drugs, although it is still present.

Because the same receptor mediates all effects of inhaled corticosteroids, the qualitative response from receptor occupancy is equal for all inhaled corticosteroids. Once a corticosteroid binds with and activates the receptor, all subsequent effects are independent of whatever drug activated the receptor in the first place. Thus, the pharmacodynamics of inhaled corticosteroids depends solely on receptor affinity, which can be determined by competitive binding assays. If equipotent concentrations are present at the receptor site, the effects are identical. Fig 3^{8,10,11} depicts the relative receptor affinities for the primary active product of the prodrug beclomethasone dipropionate, 2 available inhaled corticosteroids that are not prodrugs, and the active product of ciclesonide by using a receptor affinity of 100 for dexamethasone as the standard.^{8,10,11} Fluticasone propionate has the highest relative receptor affinity, 18 times greater than that of dexamethasone. In other words, one eighteenth the concentration of fluticasone propionate is required at the receptor to get an effect

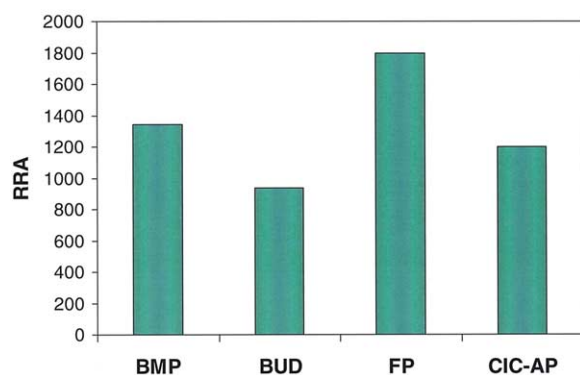


FIG 3. Relative receptor affinity (RRA) of beclomethasone-17-monopropionate (BMP), budesonide (BUD), fluticasone propionate (FP), and the active product of ciclesonide (CIC-AP). All receptor affinities are relative to that of dexamethasone, which is assigned an arbitrary affinity of 100.^{8,10,11}

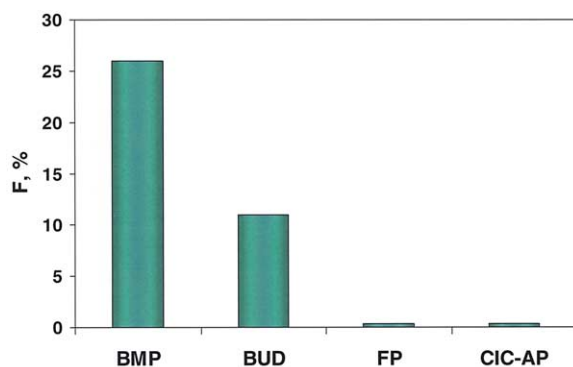


FIG 4. Oral bioavailabilities (*F*) of beclomethasone-17-monopropionate (BMP), budesonide (BUD), fluticasone propionate (FP), and the active product of ciclesonide (CIC-AP).^{10,12,13}

identical to that produced by dexamethasone. As previously discussed, beclomethasone-17-monopropionate has the second greatest receptor affinity (~13.5-fold greater than that of dexamethasone), and the active product of ciclesonide has the third highest receptor affinity (~12-fold greater than that of dexamethasone). Budesonide has slightly less receptor affinity than the active product of ciclesonide.

It is important to note, however, that relative receptor affinity in and of itself is neither good nor bad. Receptor activity is a function of both receptor affinity for a particular corticosteroid and the local concentration of that corticosteroid. Differences in receptor affinity can be compensated for by controlling the dose—and thus the concentration at the receptor site—to achieve equivalent drug effects.

Thus, because the pharmacodynamics of inhaled corticosteroids depends solely on their relative receptor affinities and because these differences can be controlled for

through dose adjustments, the major differences between inhaled corticosteroids must be due to differences in pharmacokinetics. Fortunately, recent advances in liquid chromatography/mass spectroscopy now enable measurements of very low drug concentrations, allowing these pharmacokinetic differences to be determined. Several important issues to consider when assessing the pharmacokinetics of inhaled corticosteroids include bioavailability, clearance, volume of distribution, half-life, pulmonary residence time, lipid conjugation, protein binding, and whether the inhaled corticosteroid is biologically active or is the pro-drug of a biologically active compound.

Bioavailability. A discussion of bioavailability of inhaled corticosteroids must differentiate between 2 bioavailabilities, pulmonary and oral, that together make up the total systemic bioavailability. Pulmonary bioavailability is very simple; 100% of whatever corticosteroid makes it into the lung will ultimately make it into the systemic circulation. Oral bioavailability, however, varies with the first-pass effect, which is different for each inhaled corticosteroid (Fig 4).^{10,12,13} Beclomethasone-17-monopropionate has the highest oral bioavailability (~25%), whereas both fluticasone propionate and the active product of ciclesonide do not have any significant oral bioavailability. As mentioned, total systemic bioavailability, the amount of inhaled corticosteroid that makes it into the systemic circulation, is the sum of the pulmonary and oral bioavailabilities.

Importantly, as the efficiency of pulmonary delivery increases, the relative effect of differences in oral bioavailability decreases. For example, assume there are 2 different inhaled corticosteroids, A and B. If corticosteroid A has a pulmonary bioavailability of 10% and an oral bioavailability of 10%, total systemic bioavailability will be 19% (10% pulmonary bioavailability plus 9% oral bioavailability [10% of the 90% not delivered to the lung]). Similarly, if corticosteroid B has a pulmonary bioavailability of 10% and an oral bioavailability of 0%, the total systemic delivery of inhaled corticosteroid B is 10% (10% pulmonary bioavailability plus 0%) for an A:B systemic exposure ratio of 1.9:1.

However, assume a more efficient delivery device is used to increase pulmonary delivery to 20%. In this case the total systemic delivery of inhaled corticosteroid A will be 28% (20% pulmonary bioavailability plus 8% oral bioavailability [10% of the remaining 80%]), and that of corticosteroid B will be 20% (20% pulmonary bioavailability plus 0%), thereby reducing the A:B systemic exposure ratio to 1.4:1. Similarly, if pulmonary delivery is increased to 30%, the A:B systemic exposure ratio falls to 1.2:1. Thus, as the efficiency of pulmonary delivery increases, the importance of oral bioavailability decreases.

Clearance. To reduce systemic adverse events, an inhaled corticosteroid should be eliminated from the systemic circulation as quickly as possible. Clearance quantifies drug elimination and is expressed as the volume of body fluid (in this case, blood) that is cleared of a substance per unit of time. Clearance is usually constant, and, for drugs metabolized and cleared in the liver, it is limited to

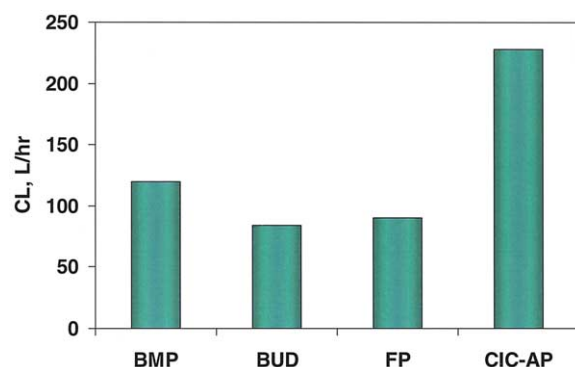


FIG 5. Apparent clearance (*CL*) of beclomethasone-17-monopropionate (*BMP*), budesonide (*BUD*), fluticasone propionate (*FP*), and the active product of ciclesonide (*CIC-AP*).¹⁰⁻¹²

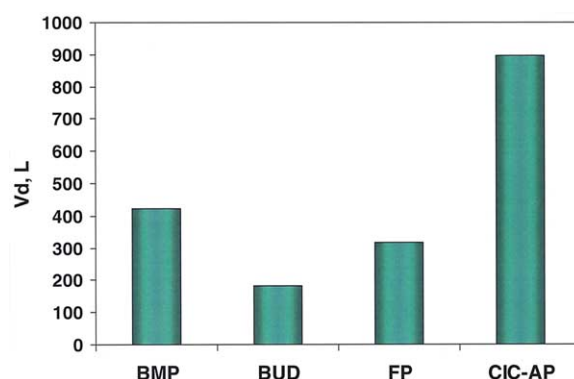


FIG 6. Volume of distribution (*Vd*) of beclomethasone-17-monopropionate (*BMP*), budesonide (*BUD*), fluticasone propionate (*FP*), and the active product of ciclesonide (*CIC-AP*).¹⁰⁻¹²

approximately 90 L/h, the rate of hepatic blood flow. All inhaled corticosteroids are cleared rapidly by the liver (~90 L/h) (Fig 5)¹⁰⁻¹²; any differences in clearance among these drugs are probably not clinically or statistically significant.

Although both beclomethasone-17-monopropionate and the active product of ciclesonide appear to have clearances that exceed 90 L/h, these clearances reflect the ratio of the actual clearance to the fraction of metabolite formed and hence might be overestimates of the true clearances. Definitive determination of the clearance of these 2 compounds would require eliminating the formation rate variable by intravenously administering the active metabolite instead of the prodrug. Nevertheless, these estimated clearances indicate that, similar to other inhaled corticosteroids, these corticosteroids are cleared rapidly by the liver. Although inhaled corticosteroids are already cleared at near maximum rate by the liver, an ideal inhaled corticosteroid could improve on this parameter through the addition of extrahepatic, as well as hepatic, metabolism and elimination.

Volume of distribution. Volume of distribution, which provides information about the distribution of the drug throughout the body, is determined by dividing the total amount of drug in the body by that drug's serum concentration. Drugs that are primarily present in tissues have low serum concentrations and thus large volumes of distribution, whereas drugs that are primarily present in blood have low volumes of distribution. Fig 6 depicts the volume of distribution for various corticosteroids, assuming complete conversion to the active metabolites for the 2 prodrugs.¹⁰⁻¹²

Fluticasone propionate and the 2 active metabolites of the prodrugs all have large volumes of distribution. A large volume of distribution indicates good tissue penetration, which suggests good penetration into the target tissues in the lung.

Half-life. Half-life is the time it takes for the concentration of a drug to decrease by 50%. A secondary pharmacokinetic parameter, it is a function of both the clearance of a drug and the drug's volume of distribution. Drugs with high clearances have short half-lives, and

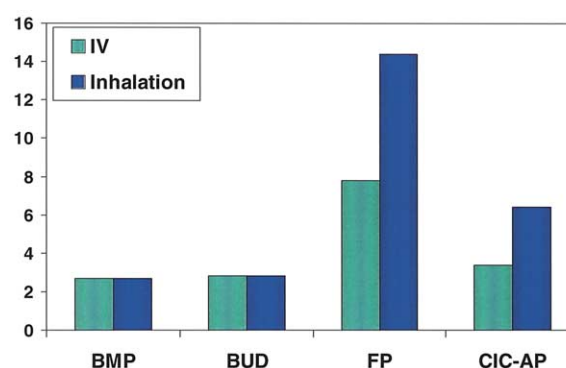


FIG 7. Intravenous (*IV*) and inhalation half-lives ($t_{1/2}$) of beclomethasone-17-monopropionate (*BMP*), budesonide (*BUD*), fluticasone propionate (*FP*), and the active product of ciclesonide (*CIC-AP*).^{10-12,17}

drugs with large volumes of distribution have long half-lives. When considering the half-life of inhaled corticosteroids, it is important to distinguish between the half-life observed after intravenous administration and that observed after inhalation, because these can differ significantly. For example, fluticasone propionate has a half-life of approximately 8 hours after intravenous administration,¹⁴ but this half-life increases to 14 hours when the drug is inhaled.^{8,15,16} Thus, after inhalation, the half-life of fluticasone propionate is no longer controlled by the actual elimination of the drug by the liver; instead, it is controlled by the rate of absorption of the drug from the lungs. This difference in half-lives between a corticosteroid administered intravenously and the same corticosteroid administered via pulmonary inhalation is an indirect way to assess the rate of absorption of that drug from the lungs. Large differences in the 2 half-lives indicate that the corticosteroid is slowly absorbed and thus retained in the lungs for long periods of time.

Fig 7 depicts the intravenous and inhalation half-lives for various corticosteroids.^{10-12,17} Similar to fluticasone propionate, the active product of ciclesonide has a signifi-

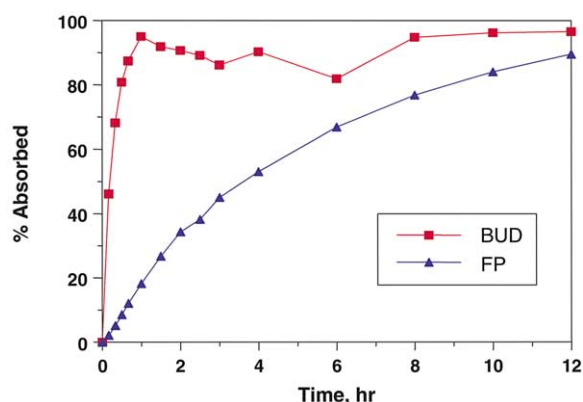


FIG 8. Absorption profiles of budesonide (BUD) and fluticasone propionate (FP).¹⁸

cantly prolonged inhalation half-life, whereas beclomethasone-17-monopropionate and budesonide have inhalation half-lives similar to their intravenous half-lives.

Half-life is sometimes misunderstood because a long half-life is intuitively associated with the danger of accumulation. However, accumulation is a function not only of half-life but also of dose and dosing interval. Just as different dosages can be used to account for differences in receptor affinities and thereby obtain equivalent drug effects, so too can different dosages, different dosing intervals, or both be used to adjust for differences in half-life and thereby obtain equivalent mean steady-state plasma concentrations.

Half-life significantly affects the plasma concentration profile. Drugs with short half-lives are cleared rapidly and therefore tend to have a greater difference between their peak and trough concentrations (ie, high peak-to-trough ratio) than do drugs with long half-lives. These differences in plasma concentration profiles can result in significant differences in drug effect, even after adjusting for differences in potency. For example, the absence of a significant trough means that corticosteroid is consistently available to occupy the receptor. Depending on the specifics of the receptor being occupied, this could result in significantly greater efficacy or significantly greater adverse effects.

Pulmonary residence time. Another way to assess the length of time an inhaled corticosteroid remains in the lung, the pulmonary residence time, is to calculate the percent absorption over time. Fig 8¹⁸ shows the absorption profiles for 2 inhaled corticosteroids. Consistent with its long half-life, fluticasone propionate is absorbed relatively slowly, with a significant amount of the corticosteroid still present in the lung 4 to 8 hours after inhalation. In contrast, budesonide disappears rapidly from the lung.

Lipid conjugation. Lipid conjugation is another important parameter in assessing the pharmacokinetics of inhaled corticosteroids. For example, close evaluation of the absorption profile of budesonide (Fig 8) shows that 100% of the drug is not absorbed; instead, absorption plateaus at 90% to 95%. Corticosteroids such as budesonide that have a hydroxyl group in the carbon-21 posi-

tion can form reversible esters with fatty acids in the lungs.^{19,20} The resultant lipid conjugate is retained in the lung and is not absorbed into the systemic circulation. Although lipid conjugates are not active, lipid conjugation increases pulmonary residence time and provides a local depot in the lung for slow release of the active compound as the conjugation bond reverses.^{19,20}

Like budesonide, the active product of ciclesonide has a hydroxyl group at the carbon-21 position and forms reversible lipid conjugates, thereby increasing the drug's pulmonary residence time and duration of action.^{11,19,20} However, the exact extent to which lipid conjugation occurs with this drug is still being evaluated. Fluticasone has a chemical structure theoretically consistent with the formation of lipid conjugates, but this has not been demonstrated to date. It is important to remember that although the formation of lipid conjugates is beneficial, only a small percentage of inhaled corticosteroid (5% to 10% in the case of budesonide) undergoes lipid conjugation; most of the drug is still systemically absorbed.

It is also important to distinguish between lipid conjugation and lipophilicity. Lipid conjugation is a true chemical bond formed between a corticosteroid and a lipid, producing an ester; this chemical bond can subsequently be hydrolyzed by enzymes, releasing the active corticosteroid. Lipophilicity, or the degree of lipid solubility of a compound, is a physiochemical property that aids the compound in crossing cell membranes. Drugs with high lipophilicity also frequently have a high degree of nonspecific binding to lipids and proteins, which leads to distribution into body tissues and results in a large volume of distribution. As a result of this large volume of distribution, drugs such as fluticasone propionate that have a high lipophilicity also have long half-lives.

Notably, studies of inhaled corticosteroids suggest that lipid conjugation is a lung-specific event. It does not appear to occur to any great extent in other tissues of the body and thus does not substantially increase the volume of distribution of the corticosteroid. Currently, the location of these lipid conjugates in the lung is not known, and it is not known whether these conjugates are intracellular or extracellular or occur in cells relevant to asthma, such as T cells or macrophages. However, even if the conjugates exist only in cells totally irrelevant to the pathology of asthma, once the conjugate is hydrolyzed, the native corticosteroid is released and again becomes available both to interact with the intracellular corticosteroid receptors in the lung and to diffuse into the systemic circulation. It is unknown what triggers this deconjugation or whether inflammation or any other pathologic process in the lung affects either conjugation or deconjugation.

Protein binding. Protein binding is another important pharmacokinetic parameter in evaluating the various inhaled corticosteroids. Most drugs bind to proteins in a reversible fashion. Unlike lipid conjugation, protein binding is not a chemical reaction but simply a physical attraction in which the drug molecule "sticks" to the protein surface. As such, it is a loose bond in which drugs can attach or detach within milliseconds.

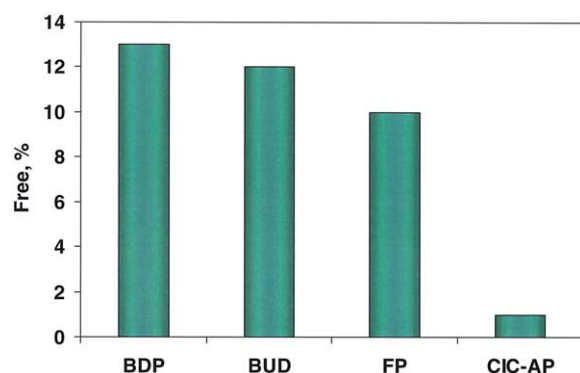


FIG 9. Percentage of free vs protein-bound component for beclomethasone dipropionate (BDP), budesonide (BUD), fluticasone propionate (FP), and the active product of ciclesonide (CIC-AP).

Protein binding is important because only free corticosteroid molecules can interact with corticosteroid receptors; protein-bound molecules are inactive. Most pharmacokinetic measurements, however, are based on the total concentration of corticosteroid, ie, the free plus the protein-bound components, and thus do not reflect pharmacologic activity. When comparing corticosteroids, it is important to consider the degree of protein binding to ensure that the comparison reflects actual pharmacologically active concentrations and not total concentrations. In previous evaluations of inhaled corticosteroids, protein binding was frequently ignored because most of the available inhaled corticosteroids had nearly equivalent protein binding. As long as 2 drugs have a similar degree of protein binding, then the relationship between their free (“active”) concentrations will be equivalent to that of their total concentrations. However, once the drugs differ in their degree of protein binding, this relationship no longer holds, and the free, non-protein-bound concentration must be determined and used in comparative trials.

The ideal inhaled corticosteroid should possess high protein binding to minimize the potential for interaction with systemic receptors leading to adverse events once the drug is absorbed from the lung. Fig 9 depicts the percentage of free versus protein-bound drug for various corticosteroids.¹⁰ Beclomethasone dipropionate, budesonide, and fluticasone propionate all have similar percentages of free drug (~10%). The active product of ciclesonide, however, is a clear outlier. More than 99% of this drug is protein bound, resulting in a greater than 10-fold difference in the amount of free drug in the circulation compared with other inhaled corticosteroids. As a result of its high protein binding, less than 1% of the active product of ciclesonide entering the systemic circulation is available for potential adverse systemic effects, compared with 10% or more for the other inhaled corticosteroids. Therefore, ciclesonide produces much less cortisol suppression than other inhaled cortico-

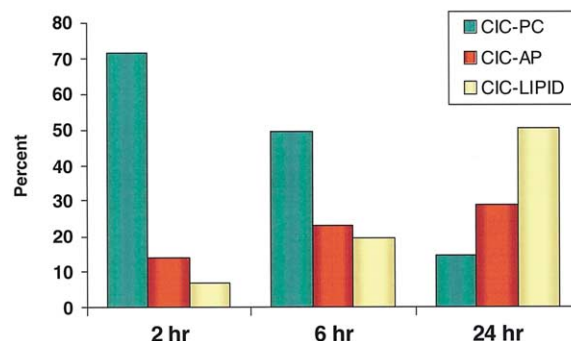


FIG 10. In vitro metabolism of ciclesonide in human lung slices. CIC-PC, Ciclesonide parent compound; CIC-AP, ciclesonide active product; CIC-LIPID, ciclesonide-lipid conjugates.

steroids^{21,22} and more closely approximates the protein binding characteristics of the ideal corticosteroid.¹¹

Initial biologic activity. Whether a compound is initially pharmacologically active also has important pharmacokinetic implications. Although prodrugs might initially be considered less attractive than other corticosteroids because they require an in vivo reaction before activation, this property actually has several potential beneficial effects. Activation of prodrugs can be targeted to the lung, minimizing oropharyngeal adverse events. Preliminary data have demonstrated that the prodrug ciclesonide is orally deposited, similar to other inhaled drugs, but unlike those drugs, this compound lacks corticosteroid activity. There is a small oral deposition of the active product of ciclesonide, but this deposition is only 4% and 8% of that seen with budesonide and fluticasone propionate, respectively. This reduction in oral deposition of active compound results in less pharyngitis/laryngitis and oral candidiasis with ciclesonide than with other inhaled corticosteroids.²³⁻²⁷

This reduction in adverse events is meaningless if the prodrug is not activated in the lung. Fig 10 (data on file, Aventis Pharmaceuticals, Bridgewater, NJ) demonstrates that ciclesonide is hydrolyzed over time to the active product in human lung slices. In addition, lipid conjugates are formed, and both the original ciclesonide and the lipid conjugates act as a slow-release pool for the supply of active product in the lung (data on file, Aventis Pharmaceuticals). Of note, although the percentage of lipid conjugates seems relatively high in these data compared with the 5% to 10% seen, eg, with budesonide, these values are not comparable, because these data were obtained in vitro, with no potential for diffusion and systemic absorption.

Properties of the ideal inhaled corticosteroid

The ideal inhaled corticosteroid thus should combine high local activity with minimal systemic adverse events, a goal that will require this corticosteroid to possess several beneficial pharmacokinetic properties. To have high local activity, the corticosteroid must have a long resi-

dence time in the lung, the only beneficial site of activity for patients with asthma. This can be accomplished in 1 of 2 ways: the corticosteroid must either have a very slow dissolution in the lung (eg, fluticasone propionate), or it must form lipid conjugates that trap it in the lung (eg, budesonide). One corticosteroid, the active principle of ciclesonide, has both properties. To produce minimal systemic adverse events, the corticosteroid must possess several additional properties. To minimize the systemic effects of any swallowed portion of the drug, the corticosteroid must have low oral bioavailability. In addition, because any corticosteroid topically deposited in the lung will eventually enter the systemic circulation, the ideal corticosteroid should have both high protein binding capability (to minimize the fraction of the drug available to interact with receptors and cause adverse events) and high systemic clearance (to quickly remove the drug from the circulatory system).

Finally, a prodrug moiety that is locally activated in the lung would be beneficial in reducing the oropharyngeal adverse events (eg, pharyngitis and candidiasis) that result from deposition of active corticosteroid in the oropharynx.

INTERPRETING STUDIES OF THE SYSTEMIC EFFECTS OF INHALED CORTICOSTEROIDS

As stated earlier, a minimal incidence of adverse events is a major component of the ideal inhaled corticosteroid. However, several pitfalls and challenges must be considered when obtaining and evaluating data on the safety of inhaled corticosteroids. Physiologic perturbations are virtually unavoidable when studying corticosteroids. Any test that is sufficiently sensitive will be able to detect a physiologic perturbation whenever a corticosteroid binds to a receptor in the body. However, this perturbation might or might not result in a persistent, significant systemic effect, and, even if it does, this systemic effect might not produce a clinically important adverse effect. Studies often confuse physiologic perturbations with adverse events because such perturbations are easier to detect and quantify; however, they are not synonymous, and it is the clinically important adverse events, not the physiologic perturbations, that are significant. With inhaled corticosteroids, it is possible to avoid these clinically important adverse events, a fact that distinguishes these agents from the long-term use of oral corticosteroids.

In reviewing studies of inhaled corticosteroids conducted during the past 10 years, a number of challenges should be considered, including study duration, the susceptibility of the study group to the particular adverse event being analyzed, excessively or inadequately sensitive tests, inaccurate or misleading dosing comparisons, compliance issues, and unrealistic expectations.

Short-term observations/long-term effects

The duration of study observation is important, because short-term observations frequently do not corre-

late with long-term effects. The effect of inhaled corticosteroids on pediatric growth is a typical example. This effect has been assessed by using knemometry, bone markers, or stadiometry in short-term studies (6 months or less); stadiometry in intermediate-term studies (12 months or longer); and stadiometry and final height analysis in long-term studies (3 years or longer). When viewed in sum, results show that in short-term studies, measures such as knemometry, although highly sensitive to the systemic effects of inhaled corticosteroids, have very low positive predictive value relative to ultimate growth suppression. For example, in a 6-week study in allergic rhinitis, Wolthers and Pedersen²⁸ used knemometry to show that intranasal budesonide significantly reduced mean lower leg growth velocity. However, there are 2 points of note concerning the study. The baseline differences in growth velocity in the children participating in the study vastly exceeded the differences in velocity detected during the course of the study. Furthermore, the greater than 90% reduction in growth velocity reported markedly exceeds reductions reported from longer 6- and 12-month trials. Thus, despite using a very sensitive measure, this short-term study greatly exaggerated the effect of budesonide on growth compared with what actually occurs during the long term.

More recent studies have used stadiometry to evaluate growth during the course of a year. This type of study is valuable in demonstrating important differences in growth effects between various inhaled corticosteroids (Fig 11).²⁹⁻³¹ However, it is still impossible to determine long-term consequences on growth from these studies, because it is unknown whether the reductions in growth represent a permanent effect or a temporary 1- to 2-year slowing in growth velocity that will ultimately be made up. Long-term effect on growth must be determined with long-term studies. The Childhood Asthma Management Program (CAMP) research group recently demonstrated the value of long-term studies in evaluating clinically relevant adverse events. In this study, children aged 5 to 12 years who had mild to moderate asthma were evaluated during a 4- to 6-year period.³² Although treatment with budesonide resulted in an initial reduction in standing-height growth velocity, this reduction was temporary and had no effect on the projected final height after adjusting for chronologic age, bone age, and pubertal status (Fig 12).³² However, the CAMP data raise another important consideration in evaluating adverse effects, namely what constitutes a clinically relevant effect. For a child who is already short relative to his or her peers, even a temporary delay in growth might be a significant adverse event. Thus, even though final adult height has been promoted as the ultimate criterion when assessing the long-term safety of inhaled corticosteroids relative to growth, it is still an imperfect measure.

It should be noted that growth is used in this section only as an example of the problem of inadequate study duration. The effect of inhaled corticosteroids on growth, as well as on other tissues and organ systems such as bone and the eye, will be discussed later in more detail.

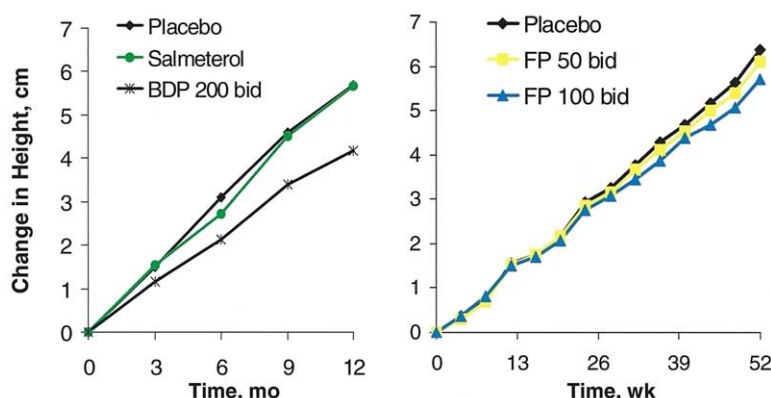


FIG 11. Mean changes in height from baseline for subjects receiving placebo (diamonds), salmeterol (circles), beclomethasone dipropionate (BDP) 200 μ g twice daily (x's), and fluticasone propionate (FP) 50 μ g twice daily (squares) and 100 μ g twice daily (triangles). In contrast to BDP, FP showed no significant effect on 1-year growth of prepubertal children. Adapted from Simons²⁹ and Allen et al³⁰ and used with permission.

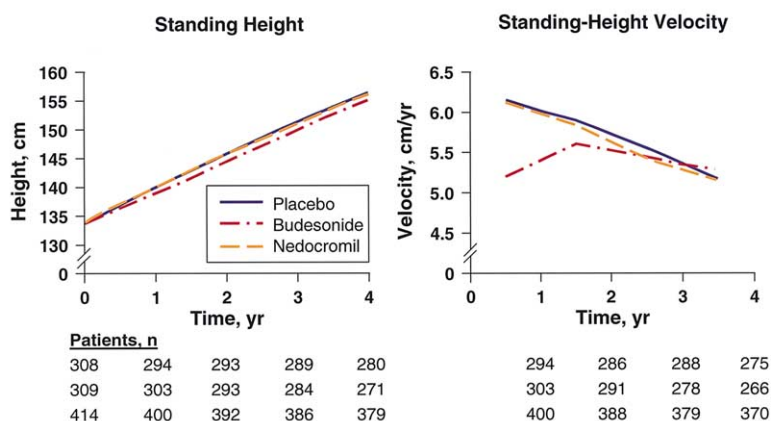


FIG 12. Mean values for standing height and standing-height velocity during 4 years of follow-up for children receiving budesonide (dot-dashed line), nedocromil (dashed line), or placebo (solid line). The numbers below the graphs represent the number of children available for evaluation in the budesonide, nedocromil, and placebo groups, respectively, at each time period. Adapted from the Childhood Asthma Management Program Research Group³² and used with permission.

Furthermore, although these data suggest that growth is not affected by long-term corticosteroid use, this finding might not apply to other tissues or organ systems in which clinically relevant adverse effects might depend on cumulative dose.

Varying susceptibility over time

When evaluating clinically relevant adverse effects, it is important to remember not only that individuals have varying degrees of susceptibility to adverse effects from corticosteroids, but also that a given individual's degree of susceptibility varies over time. Again, growth is a good example of this phenomenon. Childhood growth is not constant but instead consists of different phases. The first couple of years of life are characterized by rapid, nutrition-dependent growth. This is followed by a period of fairly slow, growth hormone-dependent growth during

the school-age years, with children experiencing their slowest rate of growth in the 2 to 3 years just before puberty (Fig 13).³³ Finally, there is a period of rapid growth that occurs during puberty before the closure of the growth plates. This period of rapid growth depends on both sex steroids and growth hormone. Susceptibility to growth suppression varies with the child's growth phase. Importantly, most studies done during the past 10 years have concentrated on children in the slow prepubertal growth phase and have ignored children in the very complicated period of pubertal growth.

Clinical significance of tests with high sensitivities

Another important issue is the sensitivity of the test used to detect the abnormality. Highly sensitive tests, although effective at getting manuscripts published, are

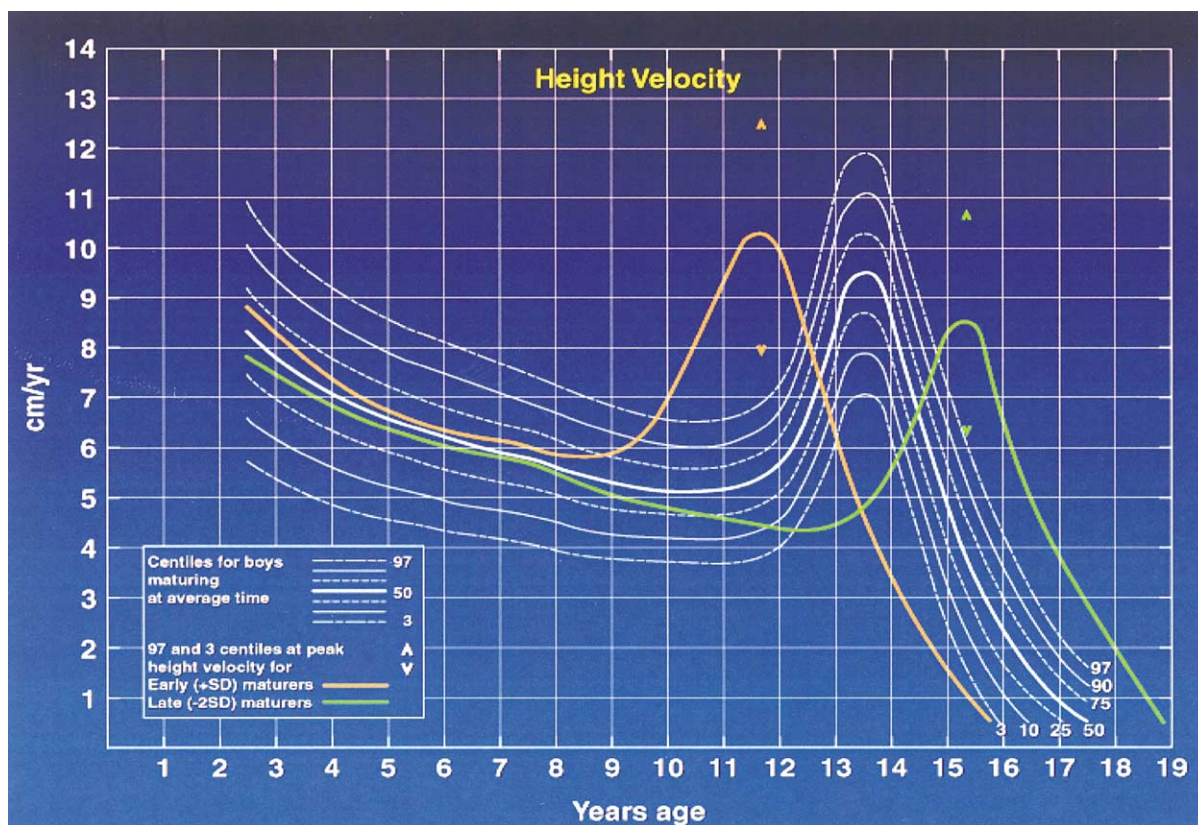


FIG 13. Height velocity curves for early-, average-, and late-maturing boys. Adapted from Tanner and Davies³³ and used with permission.

poor predictors of clinically significant long-term effects. On the other hand, insensitive tests might provide little or no meaningful information. Tests involving the hypothalamic-pituitary-adrenal (HPA) axis are a good example. During the past 10 years, there has been tremendous confusion about how to interpret these studies in terms of significant adverse events.

Urinary cortisol measurements and the area under the cortisol plasma-time concentration curve are very sensitive means of detecting any perturbation in the basal activity of the HPA axis. Replacement of endogenous cortisol by exogenous cortisol will reduce the amount of cortisol generated each day to a statistically significant degree. However, this reduction in endogenous cortisol production might have no long-term clinical significance. For example, ingestion of 2 mg of hydrocortisone at bedtime will statistically significantly reduce the area under the curve for cortisol for the next 12 hours. However, this small amount of hydrocortisone could be ingested every night without any significant effect on the HPA axis, bone mineral density, or growth. Thus, although this highly sensitive measure of HPA axis function accurately detects the presence of drug in the circulation, it has very poor predictive value in terms of risk for adrenal insufficiency.

It has been suggested that one of the advantages of highly sensitive tests is that if no effect is seen by using a highly sensitive test, there is no need to worry about any effects. However, to date, no study has been conducted to verify this with respect to inhaled corticosteroids. Furthermore, although the idea is theoretically appealing, it would apply only if the sensitive test had a true causal relationship with the adverse event. For example, a sensitive test of acute exposure might fail to correlate with adverse events related to long-term cumulative exposure.

Similarly, tests might also be inadequately sensitive to measure clinically significant adverse events. Dynamic stimulation tests evaluate the physiologic integrity of the adrenal gland. These tests have proved to be clinically useful, because adrenal insufficiency is uncommon when there is a normal ACTH stimulation test result. However, ACTH stimulation tests are not perfect; they assess only the adrenal gland's ability to respond to exogenous ACTH and not the central nervous system's ability to produce ACTH. Over time the presence of exogenous corticosteroid can result in a progressive diminution of the pituitary gland's ability to produce ACTH in response to stress. A perfectly normal adrenal gland will still produce inadequate amounts of cortisol in times of stress if

the pituitary gland does not make sufficient ACTH. However, an individual with this condition can still have a normal ACTH stimulation test response, because it does not take much endogenous ACTH to keep the adrenal glands responsive to exogenous ACTH. Thus, traditional-dose ACTH stimulation tests might be inadequately sensitive with respect to clinically significant adverse events.

For example, Tinkelman et al³⁴ evaluated growth and ACTH stimulation tests in children treated for 1 year with either beclomethasone dipropionate or theophylline. Even though ACTH stimulation test results for the 2 treatment groups were almost identical, with no child having an abnormal test result, beclomethasone dipropionate significantly ($P = .005$) reduced mean growth rate (4.2 cm/y) when compared with theophylline (5.5 cm/y).

On the basis of these results, growth was considered for many years to be the most sensitive indicator of the systemic bioavailability of inhaled corticosteroids. However, this is not true. The sensitive tests of the HPA axis, discussed earlier, are the best indicator of systemic bioavailability of corticosteroids; studies have shown that abnormalities can be detected in this axis even in the absence of detectable blood levels. This probably reflects the distribution of corticosteroids in the body, because corticosteroid that enters the central nervous system will affect the HPA axis even though it might no longer be detectable in the blood.

With respect to the study by Tinkelman et al,³⁴ a more sensitive test of the HPA axis likely would have detected the effects of the inhaled corticosteroid. Kannisto et al,³⁵ for example, evaluated adrenal suppression and growth by using a low-dose ($0.5 \mu\text{g}/1.73 \text{ m}^2$) ACTH stimulation test instead of the usual 250- μg test. Children were randomly assigned to receive budesonide (800 $\mu\text{g}/\text{day}$ during the first 2 months and 400 $\mu\text{g}/\text{day}$ thereafter), fluticasone propionate (500 $\mu\text{g}/\text{day}$ during the first 2 months and 200 $\mu\text{g}/\text{day}$ thereafter), or either cromolyn or nedocromil. Those who received budesonide had more abnormal ACTH stimulation test results and greater growth abnormality than children receiving fluticasone propionate. Overall, height scores decreased 0.4 inches in children with an abnormal result on the low-dose ACTH stimulation test, compared with only 0.08 inches in children with a normal stimulation test result.

There are several considerations, however, when evaluating studies using low-dose stimulation tests. One issue is how low the dose of ACTH should be when used in a stimulation test. Studies have shown that in individuals with a normal HPA axis, a 0.5- μg dose of ACTH is as effective a stimulant as the usual 250- μg dose. However, for practical reasons, because ACTH comes in 250- μg vials and must be diluted before the stimulation test, 1 μg is typically the lowest dose used. This dose is roughly equivalent to the amount released by the pituitary gland in response to stress and thus approximates normal physiology. Dilution of ACTH, however, introduces another problem, namely the potential variability in dose administered among centers involved in a given multicenter trial, as well as among different studies.

Finally, the differences between high- and low-dose suppression tests make it difficult for investigators to know where to draw the line between sensitivity and clinical relevance in interpreting studies of inhaled corticosteroids. One of the biggest challenges is determining what degree of HPA axis suppression is necessary before significant, clinically relevant adverse events are seen. This might be an unanswerable question. Although the HPA axis is the most sensitive indicator of systemic bioavailability, it could be that the answers with respect to clinically relevant adverse events might require focusing on the end-point physiologic processes (eg, growth) and organ systems (eg, bone and eye).

Dosing issues

Although comparisons between drugs that ignore issues such as potency and receptor binding can be very misleading, frequent studies continue to appear in the literature that fail to compare clinically equivalent dosages or to test drugs within their recommended dose range. For example, suppression of urinary cortisol was reported in a comparison of fluticasone propionate, beclomethasone dipropionate, triamcinolone acetonide, and budesonide not only on a microgram per microgram basis but also in total daily doses of up to 2 mg, which greatly exceeds the recommended dosage for these drugs.³⁶ In contrast, an earlier study with more reasonable and clinically equivalent dosages and that used creatinine excretion to correct urinary cortisol excretion values found no significant differences between budesonide and fluticasone propionate with respect to suppression of urinary cortisol excretion.³⁷

Compliance issues

Compliance is a major issue that must be considered when assessing the effect of any long-term treatment. Compliance in prospective, tightly controlled clinical trials does not accurately reflect "real world" use of inhaled corticosteroids, and, even in tightly controlled clinical trials, compliance can wane over time. These reductions in compliance must be considered in both the design of a trial and the ultimate interpretation of results.

Waning compliance might explain why long-term studies of beclomethasone dipropionate fail to detect any effect on study subjects' final height, even though tightly controlled clinical trials clearly demonstrate a height effect. In a study evaluating compliance with inhaled corticosteroids, Milgrom et al³⁸ found that although children between 8 and 12 years of age reported near 100% compliance with their medication regimen, actual compliance as determined by electronic metered-dose monitors was on average only 58%, with more than 90% of subjects exaggerating their use of inhaled corticosteroids (Fig 14). Furthermore, only 32% of those doses were actually received at the correct time. Similar observations were recently confirmed in a Scandinavian study, which demonstrated reductions in compliance to approximately 50% within 12 to 15 months of initiation of twice-daily corticosteroid therapy (Fig 15).³⁹ In evaluating previous observational studies, it is important to bear in mind that a reported

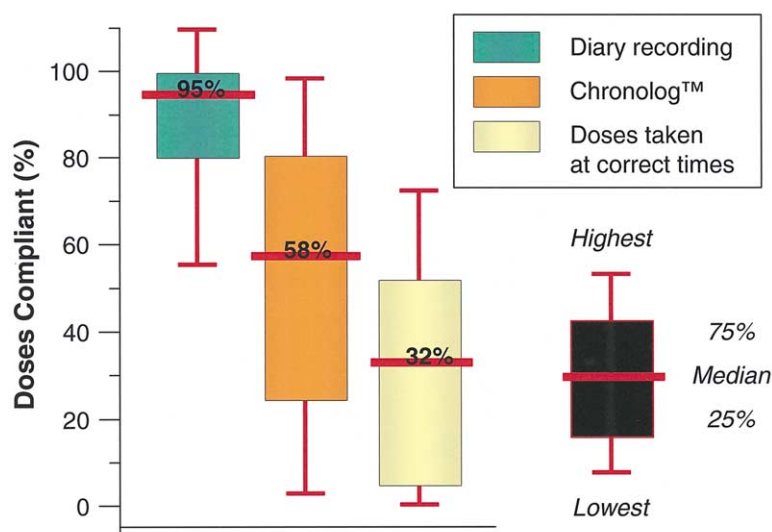


FIG 14. Compliance with inhaled corticosteroid use in children between 8 and 12 years of age. Although near 100% compliance was reported, actual compliance was less than 60% with only 32% of doses actually received at the correct time. Medians and interquartile ranges (25th and 75th percentiles) were used to summarize compliance measures across subjects because distributions were often skewed. Adapted from Milgrom et al³⁸ and used with permission.

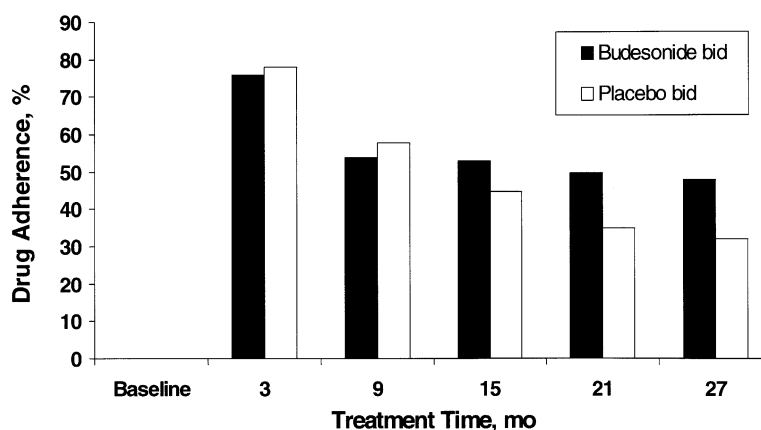


FIG 15. Measured drug adherence for use of Turbuhaler in the morning, treating mild childhood asthma with inhaled budesonide or placebo for 27 months. Adapted from Jónasson et al³⁹ and used with permission.

beclomethasone dipropionate dose of 400 µg/day probably represents an actual received dose of only 100 to 200 µg/day. Fig 16 depicts the interaction between the growth effects of inhaled corticosteroid therapy and compliance with such therapy.⁴⁰ Immediately after starting inhaled corticosteroids, compliance is very high; short-term studies have clearly demonstrated a significant adverse effect on growth during this period. Long-term studies have shown, however, that growth returns to normal over time as compliance with the inhaled corticosteroid regimen falls to between 50% and 60%.^{32,41}

Despite problems with waning compliance, long-term observational studies are very valuable to an understanding of the safety of inhaled corticosteroids in the treatment of patients with asthma, because they demonstrate that in actual clinical practice, inhaled corticosteroids reasonably control asthma symptoms while remaining relatively safe with respect to growth. However, the question of whether children are being initially overtreated remains to be answered. Many of the studies recruited subjects with mild asthma that might have been well controlled by a long-acting β-agonist or a much lower dose of inhaled

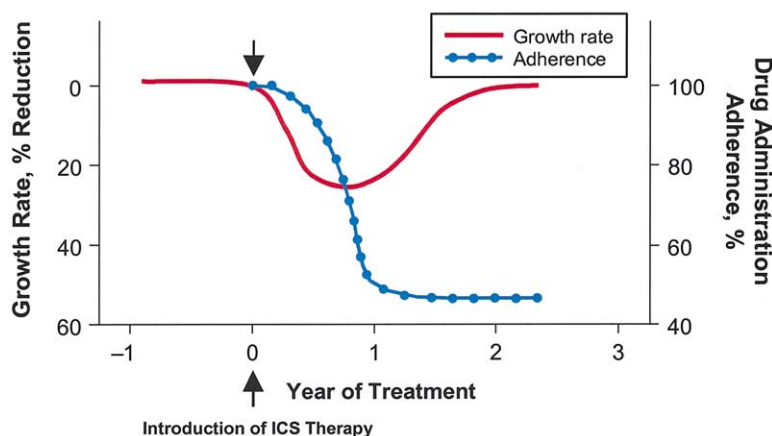


FIG 16. Interaction between inhaled corticosteroid growth effects and adherence. *ICS*, Inhaled corticosteroid. Adapted from Wolthers and Allen⁴⁰ and used with permission.

corticosteroid than initially prescribed. In addition, a confounding issue in many studies is the use of a fixed-dose model instead of titration to the lowest effective dose, thus increasing the potential for overtreatment.

Finally, it is important to note that compliance is determined by the patient and can only be monitored by the physician; in other words, compliance can be measured, but it cannot be enforced. Ultimately, compliance comes down to the patient's decision in terms of how they feel and how important they perceive the corticosteroid to be. Compliance is better in responders; the patient who believes the corticosteroid is not beneficial will tend to obtain fewer medication refills.⁴¹

Unrealistic expectations

Although there is strong incentive to avoid using any drug with adverse systemic effects, this is rarely possible with the prescription of physiologically active and effective medications. Expecting highly effective anti-inflammatory agents to have no systemic adverse events is unrealistic; furthermore, such expectations are beyond those placed on other commonly prescribed medications.

Pharmaceutical companies are partially responsible for the unrealistic expectations and misplaced focus regarding the safety of inhaled corticosteroids. Unlike antibiotics, for which efficacy and spectrum of activity are the primary concerns in demonstrations of superiority, all currently available inhaled corticosteroids are very efficacious. As a result, pharmaceutical companies often focus on safety issues to demonstrate an incremental advantage of one inhaled corticosteroid over another. Thus, it is important to place the potential adverse effects of inhaled corticosteroids into perspective, which requires making appropriate comparisons on the basis of disease severity. In patients with severe, persistent, "corticosteroid-dependent" asthma, the safety of high-dose inhaled corticosteroids should be compared with that of a viable clinical alternative, oral

corticosteroids. In such comparisons, the safety profile of inhaled corticosteroids is clearly superior to that of oral corticosteroids. However, the more prevalent and probably more important issue is safety in patients with persistent, mild to moderate asthma. In these patients, the efficacy and safety of the lowest effective dose of inhaled corticosteroid should be compared with those of noncorticosteroid medications, taking into account the risk of reliance on bronchodilators and the morbidity of poorly controlled asthma. Despite short-term growth effects, treatment with beclomethasone dipropionate has been shown to improve quality of life compared with long-acting β -agonists.²⁹ Furthermore, as previously discussed, regular use of low-dose inhaled corticosteroids decreases the risk of death, with the reduction in risk directly related to the dose of inhaled corticosteroid.⁷

These studies help put the safety issue into perspective. Inhaled corticosteroids decrease morbidity and mortality and are the most effective anti-inflammatory agent available for the treatment of asthma. Although they have dose-, drug-, and route-dependent adverse effects, these effects are known and can be monitored. Any realistic assessment of the risks and benefits of inhaled corticosteroid use in patients with asthma is heavily weighted toward the benefits. Even so, in meeting the challenge of making patients and physicians more comfortable with the use of these drugs and obtaining better compliance, emphasis should be placed on further reducing risks and developing a realistic perspective about those risks.

Summary: Evaluating clinical trial data

In summary, there are several challenges in designing and interpreting data from clinical trials assessing the adverse systemic effects of inhaled corticosteroids. The study duration and follow-up period must be adequate, because short-term observations do not equal long-term effects. There must be awareness of, and the analysis

based on, the susceptibility of the subgroup being evaluated for the particular adverse effect. This requires a thorough knowledge of developmental physiology and the resilience of various developmental systems to identify the high-risk subgroups and putting the data into proper perspective. The tests used in the analysis must be appropriately sensitive and predictive of clinically relevant end points. Tests that are either inadequately or excessively sensitive do not produce useful clinical data. Comparisons must be accurate and not misleading (ie, meaningful systemic effects can be compared only through the use of bioequivalent doses within the appropriate therapeutic ranges for the drugs being evaluated). The confounder of waning compliance over time must be factored into the data interpretation. It is also important to recognize that poor compliance in the general population might create an increased risk for those individuals who are and remain highly compliant over time. Frequently, it is these highly compliant individuals who develop adverse systemic effects from inhaled corticosteroids when they are not regularly evaluated and their dosages appropriately tapered. Finally, expectations of the results from the study have to be reasonable. It is unlikely that an asthma drug can be developed that is highly efficacious without some systemic bioavailability. This requires better education of physicians, patients and their parents, and the lay press about the true risks and benefits of inhaled corticosteroid therapy for asthma. These risks are small, can be monitored, and can be largely prevented by the rational use in and appropriate follow-up of patients receiving inhaled corticosteroids.

ASSESSMENT OF EFFECTS OF GLUCOCORTICOIDS ON BONE

Phases of normal bone mass development over time

Similar to the previous material, an understanding of the effects of glucocorticoids on bone requires an understanding of the various phases of bone development and how these phases might affect the susceptibility to corticosteroids. During the first several decades of life, bone mass increases, with humans ultimately reaching peak bone mass between ages 20 and 40 years. This accrual of bone mass depends on several factors including sex steroids, growth hormone, and a series of other factors. Starvation, poor calcium intake, or a serious systemic illness occurring early in life can all interfere with an individual's ability to achieve normal peak bone mass. Genetic factors also affect peak bone mass. Thus, when assessing osteoporosis in individuals, it is important to know the family history because this can significantly affect the risk of osteoporosis.

Once peak bone mass is achieved at about age 30 years, there is a gradual loss thereafter. This loss occurs at a slow, relatively constant rate in men. Similar to men, women start out with a gradual slow rate of loss, but between ages 45 and 50 years at the time of menopause,

this rate accelerates rapidly with subsequent continuing loss beyond menopause. The issue of acceleration of bone loss at menopause is an interesting phenomenon because it mimics what occurs when glucocorticoids are given; there is an acceleration of bone loss within the first 12 to 24 months of administration, followed by an attenuation of this effect with continued corticosteroid administration. Clinically, because of the potential for rapid loss of bone mass, menopause is a critical period for evaluation and medical intervention to slow the rate of loss in those women who either already have a low bone mass or who are at high risk for osteoporosis.

Similarly, the period of bone mass accrual is another crucial period. Because an individual gradually loses bone mass throughout most of adult life, it is important that they achieve a normal peak bone mass. Thus, when assessing the effects of corticosteroids on children, it is important to evaluate not only the effects of these agents on rate of linear growth and final adult height but also the effects on bone mineralization. If corticosteroids significantly decrease mineralization during this crucial period, reducing ultimate peak bone mass achieved, although clinically relevant adverse effects might not be initially apparent, they will likely occur decades later as a result of the normal physiologic loss in bone mass over time.

The effects of corticosteroids on adult bone is a complicated issue (pediatric issues will be discussed in greater detail later in this supplement). When comparing data, one must be aware of the specific patient populations that were evaluated in the various studies. Mixed populations that include premenopausal, menopausal, and postmenopausal women can obscure the effects of menopause. In contrast, studies limited to only premenopausal women, while eliminating a potential confounder, also eliminate a critical period of potentially increased susceptibility.

Osteoporosis: Definition and risk factors

Although osteoporosis is often thought of only in terms of bone mass, bone density alone does not account for fracture rates, and the microarchitecture of the bone is a critical factor. Therefore, osteoporosis is defined as a systemic skeletal disease characterized by compromised bone strength predisposing to an increased risk of fracture.^{42,43} Bone strength depends on 2 primary factors, bone density and bone quality. Bone density is a reflection of bone mass, and bone quality refers to the architecture, turnover, damage accumulation, and mineralization of bone.^{42,43}

The increase in fracture rate from corticosteroids is higher than expected for the degree of bone loss, suggesting that in addition to reducing bone density, corticosteroids also have an adverse effect on the microarchitecture. However, assessing these changes in bone microarchitecture typically requires sophisticated invasive studies involving biopsies.

Several important risk factors for osteoporosis are potentially confounding variables in studies evaluating the effects of inhaled corticosteroids on bone. As dis-

cussed, women experience rapid bone loss at menopause.^{42,43} Thus, both postmenopausal status and early menopause (before age 45 years) are important risk factors. Race or ethnicity is also an important risk factor. Throughout their lives, white non-Hispanic women have lower bone mineral density than black women.^{42,43} As a result of these 2 factors, white postmenopausal women have the highest age-adjusted incidence of fracture and account for almost three fourths of all hip fractures.^{42,43} Body mass index, by influencing bone density, is also an important risk factor; thin, small-framed individuals have less bone density and an increased fracture risk.^{42,43} Other important risk factors for osteoporosis include a family history of osteoporosis, smoking, and a history of a prior fracture,^{42,43} and secondary causes include genetic disorders, hypogonadal states, endocrine disorders, gastrointestinal diseases, hematologic disorders, connective tissue disease, nutritional deficiencies, and chronic systemic disorders such as congestive heart failure, end-stage renal disease, and alcoholism.^{42,43} Finally, a number of drugs, including steroids, thyroid replacement agents, and anticonvulsants (through their effect on vitamin D metabolism), also increase the risk of osteoporosis.^{42,43} Studies assessing the effect of inhaled corticosteroids on bone must account for the confounding effects of these risk factors including race, body dimension, menopausal status, and other medications.

The clinically important adverse effect of osteoporosis is the osteoporotic fracture. Bone mass accounts for approximately 70% of bone strength^{42,43} and is the single most accurate predictor of an increased fracture risk in population studies. With respect to evaluating risk for osteoporotic fracture in individual patients, however, other important factors must also be considered. A previous fracture as an adult, especially one out of proportion to the trauma, is the highest predictor of a subsequent fracture. In addition, a family history of an osteoporotic fracture is also a strong predictor of fracture. Even in individuals with a low bone mass, a fall that is traumatic is usually required to fracture a bone. Thus, the tendency to fall is a very important risk factor in the elderly, but one that can be reduced by maintaining adequate muscle strength. In fact, the reason elderly patients are often encouraged to walk to prevent fractures is not because of any effect exercise might have on bone density but because exercise helps to maintain muscle strength, thus reducing the propensity to fall. Finally, certain medications that increase the risk of fracture are those that have sedative effects, which increase the risk of fracture by increasing the risk of falling.

Corticosteroid-induced bone loss

Because reduced bone mass is a factor in osteoporotic fractures, it is important to understand the effects of corticosteroids on bone loss. Bone is a dynamic structure that is constantly forming and breaking down during adult life. When bone resorption exceeds bone formation, the individual is in a negative balance with respect to bone, and bone density declines. During menopause, although bone

formation is normal, the absence of estrogen increases bone resorption, leading to an abrupt loss in mass. Similarly, corticosteroids effectively uncouple the link between bone formation and resorption by both suppressing bone formation and increasing bone resorption. Corticosteroids have a direct suppressive effect on the activity of osteoblasts, thus directly suppressing bone formation. For this reason, serum osteocalcin levels are a sensitive surrogate marker of the effects of corticosteroids on bone.

In addition, corticosteroids produce secondary hyperparathyroidism, which leads to bone resorption. Serum calcium homeostasis is maintained by balancing calcium input through the gastrointestinal tract, calcium excretion through the kidney, and the uptake or release of calcium through net bone formation or resorption. In the gastrointestinal tract, corticosteroids reduce calcium absorption through an anti-vitamin D effect. Corticosteroids also promote renal hypercalciuria, increasing calcium loss through the kidneys. To compensate for this net calcium loss and to maintain serum calcium homeostasis, the body increases production of parathyroid hormone, which enhances the resorption of bone, releasing calcium into the circulation at the expense of bone mass.

Adrenal androgens such as dehydroepiandrosterone sulfate (DHEA-S) increase bone formation and decrease bone resorption; this effect is probably related to their conversion into active sex steroids (estradiol and testosterone).⁴⁴ Daily oral doses of DHEA-S have modest beneficial effects on bone in elderly women but not men, perhaps because the testes continue to produce testosterone throughout life.⁴⁴ In addition to suppressing the production of cortisol, exogenous corticosteroids also suppress the production of adrenal androgens, reducing the beneficial effect of these steroids on bone formation. High doses of exogenous corticosteroids (prednisone, ~20 mg/day) also decrease the production of gonadotropin-releasing hormone (GnRH). This decreases the production of luteinizing hormone (LH), which leads to a secondary hypogonadism with decreased testosterone production, further decreasing bone formation and increasing bone resorption. Thus, high doses of systemic corticosteroids produce myriad detrimental effects on bone, including direct effects on bone formation as well as secondary effects on bone formation and resorption via hyperparathyroidism, hypogonadism, and diminished adrenal androgens.

These facts suggest several logical therapies for patients receiving high doses of systemic corticosteroids. Weight-bearing activity is important to maintain muscle mass and to reduce the propensity for falling. Adequate calcium and vitamin D intake is important, especially because of the anti-vitamin D effect of corticosteroids on bone. Hydrochlorothiazide can reduce corticosteroid-induced renal calcium wasting, effectively reducing the secondary hyperparathyroidism. Estrogen and progesterone supplementation can be given to women who are experiencing postmenopausal bone loss, and testosterone supplementation can be given to men without prostate disease who have low testosterone levels. In addition,

calcitonin and bisphosphonates such as alendronate can counteract the accelerated resorptive effects of systemic corticosteroids on bone.⁴⁵⁻⁴⁹ A recent 2-year, placebo-controlled, double-blinded evaluation of alendronate found that alendronate significantly increased total body bone mineral density as well as specific densities measured at the lumbar spine and femoral neck. This increase in bone mineral density was associated with a significant reduction in the incidence of vertebral fractures (alendronate, 0.8% vs placebo, 7.1%; $P = .02$).⁴⁷ Similarly, in another recent study, calcium plus either alendronate or calcitonin increased bone mineral density compared with calcium supplementation alone; this increase in bone mineral density was associated with both a significant decrease in pain and a significant improvement in quality of life.⁴⁶ Furthermore, these findings are associated with pronounced suppression of markers of bone resorption.⁴⁵ Finally, the most critical factor in reducing the detrimental effects of corticosteroids on bone is to limit exposure. The lowest dose of corticosteroid necessary to control the disease should be used, with the inhaled formulation preferable to the oral formulation whenever possible because of the reduced systemic exposure.

Markers of corticosteroid effects on bone

Various biochemical markers of bone resorption and formation can be used to assess the effects of corticosteroids. Cross-linked N-telopeptide and pyridinium cross-links present in the collagen of bone are released into the circulation as bone is resorbed. These markers, which are excreted by the kidneys and can be readily detected in the urine, are used in women approaching menopause to detect rapid bone loss and to show suppression of that loss after treatment with either estrogen replacement therapy or bisphosphonates. They are also good markers to use when assessing the acute effects of corticosteroids on bone. In individuals receiving systemic corticosteroids, there is a short-term increase in these markers, which can be detected during the first few weeks to months of therapy. However, similar to the previously described effect of corticosteroids on growth parameters, there is attenuation of the effect of corticosteroids on these markers over time, reducing their ultimate value in assessing long-term effects. Markers of bone formation include serum osteocalcin, bone-specific alkaline phosphatase, and carboxy terminal propeptide of type I procollagen. Similar to the markers of bone resorption, these markers also show an attenuation of the corticosteroid effect over time and thus are useful in assessing acute but not chronic corticosteroid effects. Finally, levels of parathyroid hormone and urinary calcium excretion can be used as markers of intestinal calcium absorption.

In addition to these biochemical markers, bone mineral density is both an important marker of corticosteroid effect on bone and the best factor in predicting fracture risk. Bone mineral density can be measured by either dual-energy x-ray absorptiometry (DEXA) or quantitative computed tomography, which is a test that provides better quantitative information and is used frequently in

Europe. However, it also involves higher x-ray exposure, which significantly limits its use for serial evaluations. In contrast, DEXA results in only marginal x-ray exposure, less than that of a standard chest x-ray, and is the preferred method of monitoring bone mineral density in the United States. Regardless of the technique used, bone mineral density can be assessed at different sites throughout the body including the forearm, the lumbar vertebrae, and the hip. The forearm contains cortical bone, whereas the lumbar vertebrae contain trabecular bone. Cortical bone has a low turnover rate and is more likely to be affected by thyroid and parathyroid hormones. In contrast, trabecular bone has a high turnover rate and is more sensitive to the effects of sex steroids and corticosteroids. Thus, the greatest losses in bone mineral density as a result of corticosteroids and the greatest treatment effects are seen in trabecular, not cortical, bone. In addition, because the clinically relevant adverse effects from corticosteroids are vertebral fractures as well as hip fractures (older than age 65 years), these are clinically relevant sites for bone mineral assessment.

In assessing vertebral bone mineral density, the area and mineral content of each vertebra are measured. These values are summed, and the mean density is calculated by dividing the total mineral content by the total area (Fig 17, A). However, there are several potential confounders to this calculation, especially in the elderly. The calculation should not be made in the presence of overlying osteoarthritis because, although dense, this is not good, mineralized bone. Similarly, overlying aortic calcification interferes with the calculation because this mineral content is detected and included even though it is not part of the underlying bone. Finally, compression fractures lead to areas of dense bone that should not be included in determining bone mineral density. However, if care is taken to eliminate these confounders, meaningful clinical data are generally obtained. Thromboembolic disease produces a high incidence of morbidity and mortality in patients with a hip fracture and is a dreaded complication for patients older than age 65 years. Thus, clinical assessment of the hips is important in these individuals. The hip can be assessed by determining the total hip density, which includes all the bony structures, or by measuring the density at specific sites within the hip (Fig 17, B). Interestingly, the bone in the femoral neck is similar to the bone in the forearm, ie, 75% cortical bone, whereas the bone in the trochanter is predominantly trabecular bone. Thus, the hip permits simultaneous assessment of both bone types. Although total hip density, including Ward's triangle, correlates with the risk of fracture, scientific studies frequently evaluate the bone mineral density in the femoral neck or in areas within the trochanter because fractures occur in these sites when an individual falls.

Bone mineral densities are interpreted by calculating a T-score or a Z-score. As previously discussed, peak bone mass is achieved somewhere between the ages of 20 and 40 years, followed thereafter by a gradual decline for the remainder of life. The T-score, an estimate of the amount

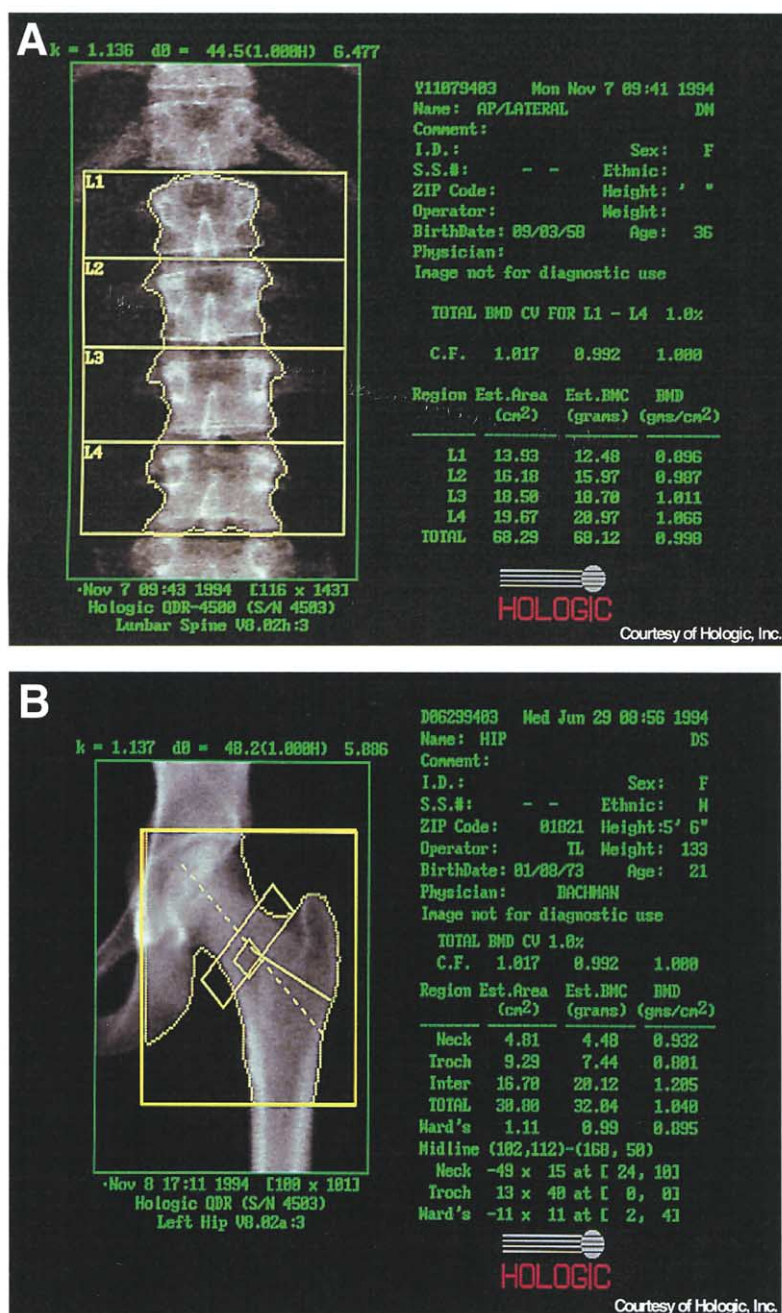


FIG 17. Calculation of bone mineral density for the lumbar spine (A) and the hip (B) by using DEXA.

of bone lost since peak bone density, is calculated by determining the number of standard deviations between an individual's bone mass and the peak bone mass of a normal young adult. Ideally, T-scores should be calculated from normative data that are both gender and ethnically correct. Factors to consider include gender and ethnicity; men have a greater peak bone density than women, and black women have a greater peak bone density than white women,⁴³ who in turn have a greater peak

bone density than Asian (ie, Japanese) women. In contrast to the T-score, the Z-score represents the number of standard deviations between an individual's bone mass and that of an average person of their current age. A Z-score is helpful in detecting significant deviations from what is expected for age; an abnormal Z-score might represent a significant underlying disorder such as multiple myeloma. However, the T-score, the amount of bone mass lost since peak bone density, correlates with frac-

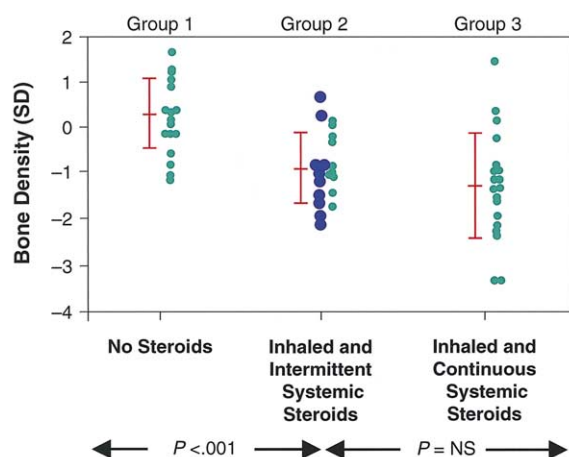


FIG 18. Bone density in 3 groups of asthmatic subjects expressed as Z-scores. Horizontal bars represent the mean values and vertical bars the standard deviation. In the inhaled and intermittent systemic corticosteroid group, large circles represent those subjects who had not received systemic corticosteroids during the past year and small circles those subjects who had received both inhaled and systemic corticosteroids during the past year. Reprinted from Packe et al⁵⁹ and used with permission.

ture risk and is used to define osteoporosis. At the spine and hip, the risk of fracture increases by 1.9-fold and by 2.4-fold, respectively, for each standard deviation reduction in bone mass.⁵⁰ By arbitrary World Health Organization definition, a T-score of at least -2.5 is osteoporosis, a T-score between -1 and -2.5 is osteopenia, and all other T-scores are normal.⁵¹

Effects of oral corticosteroids on bone loss

Although the main clinically relevant adverse effect with corticosteroids on bone is osteoporotic fracture, these data are limited, especially in relation to inhaled corticosteroids for which there are very few, if any, data. The surrogate end point used in most studies is bone mineral density. With respect to oral corticosteroids, corticosteroid-induced bone loss correlates with daily drug use, the duration of use, and the cumulative lifetime dose.^{52,53} Thus, these 3 factors significantly affect the risk of both osteoporosis and osteoporotic fractures. Individuals who are cushingoid as a result of long-term oral corticosteroid use have an approximate 50% fracture rate.⁵⁴ In fact, the threshold for this effect is quite low. Doses of prednisone as low as 7.5 mg/day have been clearly associated with the development of osteoporosis.⁵³ Moreover, this threshold dose might be size dependent. In a small-framed individual with a small amount of body water, prednisone 5 mg/day during a prolonged period of time might be sufficient to cause osteoporosis.⁵² Thus, even corticosteroid doses that are generally considered safe “replacement” doses for most people might carry a significant risk for osteoporosis in others. Similar to what is seen during menopause, patients receiving oral corticosteroids have the greatest degree of bone loss during the first 12 to

24 months of therapy, with attenuation in the rate of bone loss thereafter.^{55,56} Trabecular bone is affected more than cortical bone, although both types of bone are affected and the difference might not be as great as previously suspected.⁵⁷ Finally, it was initially thought that every-other-day corticosteroid therapy, which would allow the HPA axis to reactivate, would be protective, but when the effects of this dosing schedule on bone were assessed by using bone density measurements, no protective effect was seen.⁵³ This might be a result of the fact that even every-other-day corticosteroid use adds to the patient’s cumulative exposure; thus, even at relatively low, “safe” doses, oral corticosteroids have significant adverse effects on bone.

Effects of inhaled corticosteroids on bone

Few data are available about the effects of inhaled corticosteroids on bone, and much of those that are have significant limitations. Because of the length of time that inhaled corticosteroids have been available, good long-term data on fracture risk do not exist. Although some studies have looked at so-called prevalent fractures (ie, fractures in which you can detect wedging of vertebrae sequentially over time),⁵⁸ these might not be relevant to the typical clinical adverse events, namely hip and vertebral fractures. There are very few placebo-controlled prospective trials. Although the corticosteroid dose is crucial with respect to adverse systemic events, very few trials have compared the effects of low and high doses of inhaled corticosteroids. Most current data come from cross-sectional studies of the effects of inhaled corticosteroids on bone density, and results of these studies are often confounded by issues of prior oral corticosteroid use, variability of baseline bone mass, and duration of therapy. Moreover, most of these studies do not control for subgroups of subjects at risk. If two thirds of subjects in a study are premenopausal women and only one third are postmenopausal, critical data relevant to the subjects at greatest risk (ie, postmenopausal women who are estrogen deficient and not receiving estrogen replacement therapy) could be lost when the means of the results are obtained. Several cross-sectional studies are reviewed here to highlight some of these problems.

With cross-sectional data, Packe et al⁵⁹ evaluated bone mass in 3 age-matched groups of asthmatic subjects. Group 1 included subjects who had never received oral or inhaled corticosteroids; group 2 included subjects who received high-dose beclomethasone dipropionate (1000 to 2000 μ g/day) for at least 1 year (range, 1 to 7 years; median, 3 years) and who had received systemic corticosteroids in the past; and group 3 included subjects receiving high-dose inhaled corticosteroid plus low-dose prednisolone (median dose, 7 mg/day). Bone mineral density in group 2 (127.5 mg/mL) was significantly reduced compared with that in group 1 (160.4 mg/mL) and similar to that in group 3 (114.5 mg/mL) (Fig 18).⁵⁹ A major problem with this study was the confounding effects of systemic corticosteroids in group 2. All subjects received systemic corticosteroids in the past, and half of them were still receiving intermittent bursts of

systemic corticosteroids during the study. The number of bursts, the duration of the bursts, and the cumulative dose of systemic corticosteroids received by subjects in this group were unknown. Given the significant known negative effects of systemic corticosteroids on bone density, it is impossible to determine from these data whether high-dose inhaled corticosteroids had any actual effect on bone density. Furthermore, even if inhaled corticosteroids did affect bone density in this study, any previous or ongoing exposure to systemic corticosteroids resulting in upregulation of receptors responsible for the adverse effects of corticosteroids could have artificially magnified this effect. This confounder of prior systemic corticosteroid exposure potentially affects all the cross-sectional studies. In addition, a difference in disease severity is another potential problem with the study by Packe et al.⁵⁹ Patients with intermittent asthma, who do not require anti-inflammatory agents, have a much milder form of disease than patients with persistent asthma, who do require either inhaled or oral anti-inflammatory agents; this difference in disease severity can have a significant effect on bone mineral density. Thus, the differences in bone mineral density detected between group 1 and groups 2 and 3 might in part be a reflection of differences in disease severity, not corticosteroid use.

In another cross-sectional study, Wong et al⁶⁰ evaluated the relationship between cumulative dose of inhaled corticosteroid and bone mineral density in the lumbar spine and proximal femur. Subjects were asthmatic men ($n = 77$) and premenopausal women ($n = 119$) ages 20 to 40 years who had used inhaled corticosteroids regularly for at least the past 6 months (median duration, 6 years) and who had limited exposure to systemic corticosteroids. Subjects who received either oral or parenteral steroids during the past 6 months or more than 2 courses of oral or parenteral steroids in their lifetime and subjects who had used more than 10 inhalers of a nasal corticosteroid or 10 prescriptions of a dermal corticosteroid were excluded. All inhaled corticosteroids were treated as equipotent without correction for formulation, inhaler, or use of spacer device. The cumulative inhaled corticosteroid dose was calculated: Mean daily dose $\times$ Duration of inhaled corticosteroid use in years $\times$ 365. Bone mineral density was measured in the spine (L2 to L4) and proximal left femur by DEXA, and a multiple linear regression analysis was used to assess the relationship between cumulative dose and bone mineral density. Fig 19 shows the study results for the lumbar spine, in which each doubling of the cumulative dose of inhaled corticosteroids was associated with a 0.16 standard deviation decrease in bone mineral density; similar results were seen for the neck of the femur, Ward's triangle, and the trochanter. At this rate, compared with a patient receiving 200 μ g/day of inhaled corticosteroids for 1 year, a patient receiving 2000 μ g/day for 7 years (approximately 5000 mg cumulative dose) would have a bone density that is 1 standard deviation lower and a risk of fracture 2-fold higher. The results of this study suggest that even a mild effect of inhaled corticosteroids on bone density in pre-

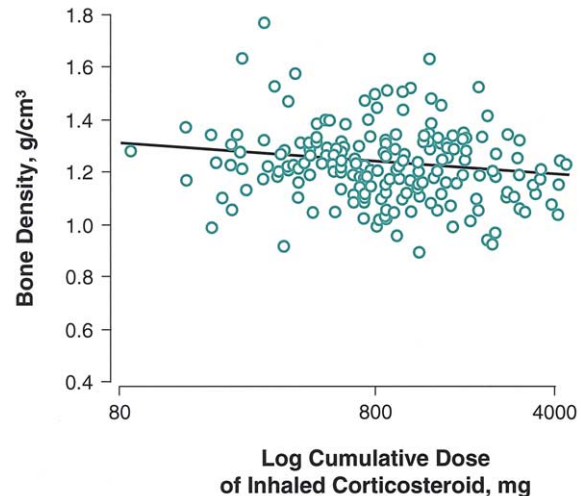


FIG 19. Scatter plot and regression line derived from age- and gender-adjusted model demonstrating a significant inverse relationship between cumulative dose of inhaled corticosteroid and bone mineral density for region L2–L4 of the lumbar spine. Adapted from Wong et al⁶⁰ and used with permission.

menopausal women can result in a significant reduction when treatment is sustained for a prolonged period of time. Although there might be no clinical consequences of this reduction early on, it can lead to a significant risk of osteoporosis and osteoporotic fractures later in life when combined with the physiologic losses that occur during and after menopause.

This study has several strengths and weaknesses. The study evaluated subjects in a primary care setting who had mild asthma with minimal or no use of oral corticosteroids. Because median exposure was 6 years, the study evaluated long-term effects, and because it was limited to a young adult population, it minimized the confounding effects of age and menopausal status. The effects seen in this study occurred in individuals who otherwise should have had relatively normal bone densities. However, the study was also cross-sectional. Thus, the bone mineral densities of the subjects before starting corticosteroids are unknown, as are their actual bone mineral losses. Because the study was questionnaire based, compliance was not assessed. Thus, the calculated cumulative corticosteroid doses might not be a true reflection of the actual doses received by the subjects. Finally, treating all inhaled corticosteroids as equipotent is a significant weakness. The effects of these drugs on the HPA axis, bone, and growth are not equivalent on a milligram basis; studies suggest that the effects on bone of beclomethasone dipropionate are much greater than those of fluticasone propionate.^{61,62}

Limited prospective data have recently become available. In a 2-year prospective study, Tattersfield et al⁴² evaluated changes in bone mineral density in subjects

TABLE I. Mean yearly changes in bone density associated with inhaled triamcinolone acetonide (100 µg/puff)*

	All women (n = 109)		Women not treated with oral or parenteral glucocorticoids (n = 83)	
	Adjusted yearly change (g/cm ² /puff ± SE)	P value	Adjusted yearly change (g/cm ² /puff ± SE)	P value
Total hip	-0.00048 ± 0.00018	.008	-0.00041 ± 0.00020	.047
Trochanter	-0.00042 ± 0.00017	.01	-0.00047 ± 0.00019	.02
Femoral neck	-0.00017 ± 0.00028	.54	-0.00015 ± 0.00031	.63
Spine (L1–L4)	-0.00012 ± 0.00018	.51	-0.00015 ± 0.00019	.41

*Yearly changes adjusted for age, oral contraceptive use, and the use of inhaled and oral glucocorticoids where appropriate. Adapted with permission from Israel et al.⁵⁸

with mild asthma randomized to budesonide (n = 87), beclomethasone dipropionate (n = 74), or noninhaled corticosteroid therapy (n = 78). Changes in bone mineral density were similar between the 3 groups, although this might have been related to poorer asthma control and a greater need for oral corticosteroid bursts in subjects not receiving inhaled corticosteroids, as well as the confounding effect of oral corticosteroid bursts in the other 2 groups. Despite this limitation, there was a significant correlation between the change in bone mineral density in the lumbar spine and the mean daily dose of inhaled corticosteroid. Furthermore, this change was not related to changes in biochemical markers of bone metabolism.

Israel et al⁵⁸ performed a 3-year prospective evaluation of the effects of inhaled corticosteroids on the rate of bone loss in 109 premenopausal women. Subjects were between the ages of 18 and 45 years and had 10 or more menstrual periods during the preceding year; furthermore, subjects were dropped from the study if menopause occurred during the course of the trial. In addition, subjects were excluded from the study if they had received any oral or parenteral corticosteroids in the preceding 3 months or more than 2 short courses (lasting 2 weeks or less) in the preceding year and were dropped from the study if they accumulated more than 30 days of systemic corticosteroid exposure during the course of the 3 years. Calcium and vitamin D intake was supplemented when necessary to ensure adequate daily intake throughout the study. Subjects were divided nonrandomly into 3 groups on the basis of their use of inhaled corticosteroids at baseline: none, low dose (4 to 8 puffs/day), and high dose (more than 8 puffs/day). Biochemical markers (serum osteocalcin, parathyroid hormone, urinary N-telopeptide, and urinary and serum cortisol) were prospectively monitored, and bone mineral densities were determined by using DEXA at baseline and after 6, 12, 24, and 36 months. This study found that bone density at both the total hip and trochanter significantly declined 0.00048 and 0.00042 g/cm², respectively, for each puff/day of inhaled corticosteroid used for every year of treatment; no dose-related effect was seen in the femoral neck or spine. Furthermore, excluding all women who received any oral or parenteral corticosteroid during the course of the study did not significantly

affect these results (Table I). There was no relationship between the biochemical markers and either the dose of inhaled corticosteroids or the decline in bone density. Because the study was not randomized, it has a number of limitations. Randomization tends to control for known and unknown confounders, and selection bias is known to occur in nonrandomized studies. The differences seen in baseline characteristics in this study depict an uneven distribution of potential confounders, which could account for the association seen. Generally, when treating asthma, disease severity is associated with number of puffs of inhaled corticosteroid prescribed; thus, differences in asthma severity could have made these groups heterogeneous, rendering them noncomparable and explaining the findings in part despite the similar lung function seen at baseline.⁵⁸ Because of these findings, the investigators recommended that inhaled corticosteroid use be limited to the lowest dose necessary to control symptoms, that bone density be periodically assessed, and that, when necessary, prophylactic measures be instituted to protect the skeleton.⁵⁸ Moreover, data obtained from a particular inhaled corticosteroid study might not be generalizable to data of another inhaled corticosteroid or to the same corticosteroid given via a different device or route (eg, intranasal route), because the effect of the glucocorticoid molecule depends on the mode of delivery. Thus, one must be careful about conclusions drawn from single individual steroid trials.

Summary of effects of inhaled corticosteroids on bone

In summary, with respect to bone, long-term use of oral corticosteroids clearly causes both mineral loss and fractures. Although few data are available on the effects of inhaled corticosteroids, these agents clearly have a better safety profile, albeit with minimal to modest effects on bone. These effects depend on both the dose and duration of therapy and might represent a cumulative dose effect. Data suggest that the various inhaled corticosteroid preparations have some differences in these effects, but the cause and exact extent of these differences are unknown. Physiologic changes that occur during menopause might make menopausal and postmenopausal women an espe-

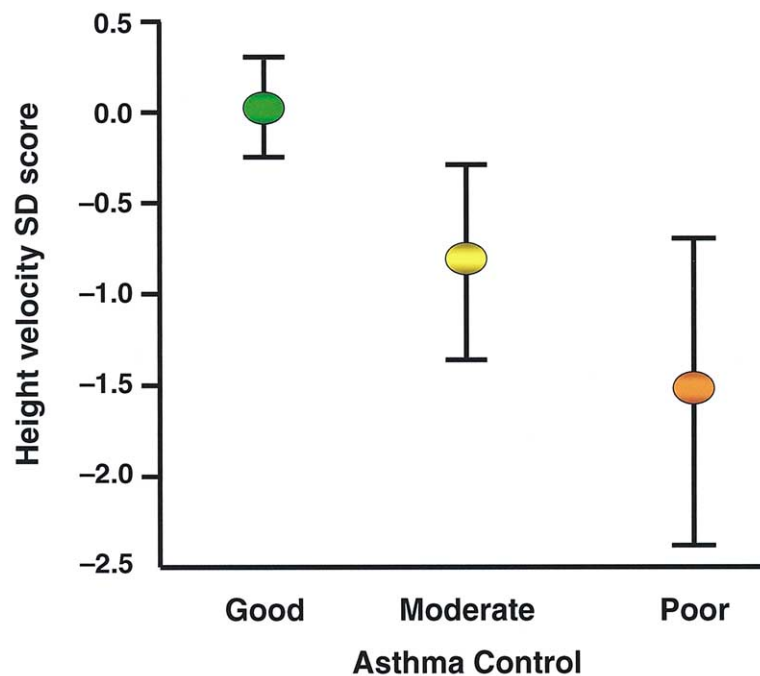


FIG 20. Effect of asthma control on height velocity standard deviation in children with asthma before receiving inhaled corticosteroids. Circles represent the mean values, and bars the 95% CI. Adapted from Ninan and Russell⁶³ and used with permission.

cially “at risk” population, but these data are also lacking. Similarly, data on the effects of other confounding risk factors, such as low body mass or family history of osteoporosis, are lacking. Perhaps because of blunting of the physiologic effects over time, biochemical markers fail to show a significant correlation with either inhaled corticosteroid dose or bone mineral loss. Serial assessment of bone mineral density is currently the best way to evaluate the effects of inhaled corticosteroids on bone. Finally, no specific data are available on the long-term effects of inhaled corticosteroids relative to fracture rates later in life. However, because fracture rates have been correlated with reductions in bone mineral density in other settings and inhaled corticosteroids reduce bone mineral density in a dose-dependent fashion, it is important to use the lowest effective dose of inhaled corticosteroids to limit ultimate bone exposure.

EFFECT OF INHALED CORTICOSTEROIDS ON GROWTH IN CHILDREN

Conditions influencing growth in children

A number of drug-related and non-drug-related confounding variables must be considered before one can evaluate the effect of inhaled corticosteroids on growth in children with asthma. Poor asthma control, in and of itself, adversely affects growth. The positive effect of corticosteroids on asthma control can potentially offset

any negative effect they have on growth. Ninan and Russell⁶³ evaluated growth in prepubertal children with asthma for a minimum of 1 year before and after starting inhaled corticosteroids. Before using inhaled corticosteroids, the children received β_2 -agonists, theophylline, or sodium cromoglycate. Asthma control was assessed by a symptom score based on the frequency, duration, and severity of symptoms and the need for rescue medication. Height velocity was inversely correlated with asthma control both before (Fig 20) and after institution of inhaled corticosteroids, with the dose of inhaled corticosteroid used having no demonstrable effect.

However, the effect of asthma on growth is even more complicated than this. Growth in children is not a constant, and girls and boys differ. Susceptibility to the growth effects of asthma vary throughout childhood with periods of both growth delay and catch-up growth. As mentioned earlier, vulnerability to growth effects of inhaled corticosteroids and other medications is likely to be greatest in the 2 to 3 years before puberty. Growth suppression in children with asthma was demonstrated as early as 1981; there was little difference in height at age 10 years, but differences in height became evident by age 14 years. Catch-up growth occurred so that by 21 years of age, height was not significantly different from that of control subjects.⁶⁴ In most studies, boys appeared more susceptible to growth suppression than girls,^{34,65,66} most likely related to the more profound prepubertal slowing in growth rate that occurs in boys.

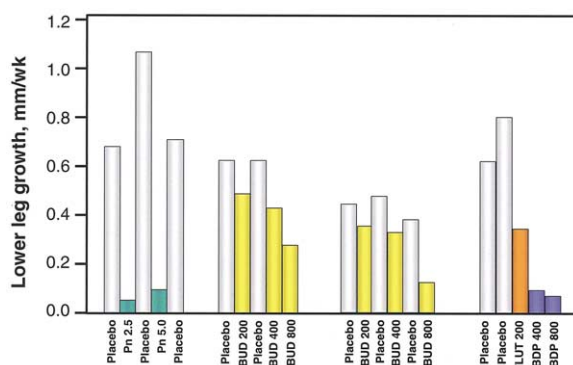


FIG 21. The effect of corticosteroids on lower leg growth as determined by knemometry.⁶⁹⁻⁷³ Pn 2.5, 2.5 mg oral prednisolone daily; Pn 5.0, 5.0 mg oral prednisolone daily; BUD 200, 200 μ g budesonide daily; BUD 400, 400 μ g budesonide daily; BUD 800, 800 μ g budesonide daily; FLUT 200, 200 μ g fluticasone propionate daily; BDP 200, 200 μ g beclomethasone dipropionate daily; BDP 400, 400 μ g beclomethasone dipropionate daily; BDP 800, 800 μ g beclomethasone dipropionate daily.

Asthma that begins in childhood is frequently associated with allergies; in fact, atopy is one of the strongest predisposing factors in the development of asthma,¹ and atopy itself increases the risk of short stature by 2- to 5-fold.⁶⁷ This might explain why atopic asthmatic subjects have a significantly greater retardation of skeletal growth than nonatopic asthmatic subjects.⁶⁷ Furthermore, this growth retardation occurs even in mild forms of atopic disease such as allergic rhinitis, suggesting that it is a disease- or genetic-specific factor and not simply the effect of a chronic disorder on growth.⁶⁷ The cause of short stature in atopic individuals might be due to the effects of platelet-activating factor. Platelet-activating factor is one of the strongest mediators in the pathogenesis of atopic disorders, and this factor also directly influences the synthesis of prostaglandin E₂, an important growth factor for bone.⁶⁷

Finally, the treatment of asthma might at times require rescue bursts of systemic corticosteroids. Systemic corticosteroids inhibit growth at multiple levels by inhibiting pulsatile secretion of growth hormone, decreasing insulin-like growth factor-1 bioavailability, decreasing the expression of growth hormone receptors, decreasing endogenous production of adrenal and androgen hormones, and decreasing collagen synthesis.⁶⁸ Therefore, any evaluation of the effects of inhaled corticosteroids on growth in children must consider the known confounding effects of poor asthma control, allergies, and systemic corticosteroid exposure.

Inhaled corticosteroid preparation confounders

Any evaluation of the effects of inhaled corticosteroids on growth is complicated by the multiple forms available. The 5 inhaled corticosteroids currently available in the United States vary greatly with respect to available

dosages, comparative efficacy, and safety. In addition, the way the inhaled corticosteroids are delivered to respiratory tissue varies between drugs and even for a single agent. Even something as simple as changing the propellant used to deliver the corticosteroid, let alone changing from one delivery system to another, can significantly affect the pattern of pulmonary distribution and the potential for systemic absorption. Despite all the research done in this field during the past 10 years, no well-established model exists for comparing the effects of inhaled corticosteroids or the effects of delivery systems.

Studies evaluating the impact of inhaled corticosteroids on growth

As already mentioned, the effects of corticosteroids on growth have been assessed in a variety of studies that vary in both technique and duration. Short-term studies use knemometry, whereas intermediate- and long-term studies use stadiometry and, ultimately, final adult height.

Knemometry is a complex technique in which the length of the lower leg from the top of the knee to the bottom of the foot is determined under conditions of a fixed constant pressure. The technique requires significant training and experience to perform accurately and thus is used in only a few laboratories. Before the 1990s it was believed that inhaled corticosteroids were delivered to and metabolized in the lung and thus did not affect growth. In the early 1990s this belief was disproved in a pediatric study in asthma by Wolthers and Pedersen,⁶⁹ who used knemometry to demonstrate that inhaled budesonide was associated with significant dose-related reductions in growth velocity, with mean reductions of 0.11, 0.17, and 0.36 mm/wk for the 200-, 400-, and 800- μ g doses, respectively. Multiple studies have subsequently confirmed this dose-related short-term effect of inhaled corticosteroids on growth, although the effect is less than that seen with systemic corticosteroids (Fig 21).⁶⁹⁻⁷³ Knemometry studies have also suggested a reduction in the effect of inhaled corticosteroids on growth when the drug is given once daily in the morning; in a comparison of growth during treatment with budesonide at dosages of 400 μ g twice a day or 800 μ g every morning, only boys treated with 400 μ g twice a day showed significant short-term growth suppression.⁶⁵ More recent data have demonstrated that this short-term growth reduction is a result of corticosteroid suppression of types I and III collagen turnover.⁷⁴

In contrast to these short-term findings, Merkus et al⁶⁶ assessed growth during a median of 22 months in asthmatic adolescents randomized to receive albuterol plus either placebo or inhaled budesonide and compared growth rates with those of control subjects matched for gender, age, height, and duration of follow-up. Male, but not female, subjects from both treatment groups had significant reductions in growth rate compared with control subjects; however, the observed mean case-control difference between treatment groups demonstrated less growth reduction in subjects receiving inhaled corticosteroids than in those receiving placebo. Thus, consistent with the

previous data that asthma itself negatively affects growth, these data were interpreted as demonstrating a reduction in growth rate and a delay in the onset of puberty as a result of asthma, not inhaled corticosteroids.

As previously discussed, Tinkelman et al³⁴ conducted the first 1-year study to demonstrate the detrimental effect of inhaled corticosteroids on mean growth rates, confirming the short-term knemometry findings. Similar to the findings of Merkus et al,⁶⁶ this effect was seen only in men and occurred predominantly in the prepubescent subgroup.³⁴ Subsequent 1-year studies by Simons²⁹ and Verberne et al⁷⁵ compared the effects of beclomethasone dipropionate and salmeterol and found that although beclomethasone dipropionate was more efficacious in controlling asthma, it significantly reduced growth. In the study by Verberne et al,⁷⁵ growth decreased 0.28 standard deviation scores with beclomethasone dipropionate, compared with 0.03 standard deviation scores with salmeterol ($P = .001$) (Fig 22). In contrast, another 1-year study found no effect on growth with fluticasone propionate.³⁰ However, this was a low-dose study, and there appeared to be a trend for reduced growth rate with increasing dose. Furthermore, this study was done with the Diskhaler, a delivery device no longer in use³⁰; thus, the results might not be generalizable to current fluticasone propionate delivery devices.

In evaluating the effects of inhaled corticosteroids on growth, the means used to present and analyze the data must be considered, because this can also significantly affect the conclusions. Although clinicians are accustomed to evaluating growth in terms of growth curves, ie, height relative to age, the US Food and Drug Administration has focused on the effects of inhaled corticosteroids on growth velocity.⁷⁶ Current data published by the Centers for Disease Control⁷⁷ show that before puberty, linear growth occurs at a constant rate of 6.41 cm/y (95% CI, 6.35 to 6.46 cm/y) in girls and 6.12 cm/y (95% CI, 6.06 to 6.17 cm/y) in boys (Fig 23⁷⁸). It cannot be determined from the figure whether the inhaled corticosteroid mildly depresses growth in all children or whether it has no effect on some children and a severe effect in others. Either can yield the same mean.

The CAMP study was a placebo-controlled evaluation of the effects of budesonide (200 µg twice daily) and nedocromil (8 mg twice daily) in children with mild to moderate asthma who were between the ages of 5 and 12 years at enrollment.³² The study was conducted in 4 phases: screening and baseline, 4 to 6 years of treatment, transition/washout, and long-term follow-up. The last phase was not part of the original study design but was added to determine the ultimate effects of inhaled corticosteroids on growth and lung development. CAMP results demonstrated that compared with nedocromil or placebo, budesonide improved airway responsiveness and provided better asthma control. As previously discussed, CAMP showed a significant reduction in growth velocity in the first year of budesonide treatment, followed by a return to normal growth velocities thereafter. The data are currently being analyzed to determine whether this return to normal

growth velocity is associated with a decrease in compliance with duration of treatment. Consistent with the 1-year reduction in growth velocity, the mean increase in height during the study was 1.1 cm less in subjects receiving budesonide than in those receiving placebo.³² However, even this difference disappeared when final adult height was projected by using current height, chronologic age, and bone age, as well as age at first menses for girls.

This projection of normal final adult height is supported by data from Silverstein et al⁷⁹ and Agertoft and Pedersen.⁸⁰ In a retrospective case-control evaluation of adults from Rochester, Minnesota, Silverstein et al found that the adult height of subjects with asthma, corrected for mid-parental height, was unaffected by corticosteroid treatment and not significantly different from that of nonasthmatic control subjects. Similarly, Agertoft and Pedersen evaluated the final adult heights of 142 patients enrolled in a prospective evaluation of budesonide. The mean duration of budesonide treatment before attainment of adult height was 9.2 years. Similar to the CAMP data, findings from this study showed that budesonide caused an initial reduction in growth velocity from 6.1 cm/y during the run-in period to 5.1 cm/y during the first year of treatment, with a subsequent turn to normal growth velocity (5.9 cm/y) by the third year of treatment. Despite this initial reduction, final adult height was not affected. The mean difference between actual and expected adult height, calculated from the mid-parental height, was +0.3 cm (95% CI, -0.6 to +1.2 cm).

It is also probable that time of day of inhaled corticosteroid administration affects the likelihood of growth suppression. In prepubertal children, pulsatile growth hormone secretion occurs primarily at night, commencing at a time when endogenous cortisol effects are usually at their nadir. Given the suppressive effect of glucocorticoid excess on growth hormone secretion, administration of exogenous corticosteroid at bedtime might be expected to have a greater effect on growth than administration in the morning, when cortisol levels are normally higher. In fact, knemometry studies of children receiving 200 µg intranasal budesonide twice a day showed clear growth suppression,⁸¹ whereas 400 µg intranasal budesonide given once a day in the morning did not.⁸² In another short-term knemometry study of children with asthma, administration of 800 µg budesonide every morning was not associated with detectable effects on growth, although 400 µg twice a day was.

Differences between inhaled corticosteroids and systemic effects

Data from both CAMP³² and Agertoft and Pedersen⁸⁰ suggest that inhaled budesonide therapy for asthma does not affect final adult height. These data, however, might not be generalized to other inhaled corticosteroids because of the significant differences in strength, comparative efficacy, safety, systemic exposure, and delivery device between the various agents. The Asthma Clinical Research Network (ACRN) has been evaluating differences in effects between the various inhaled cortico-

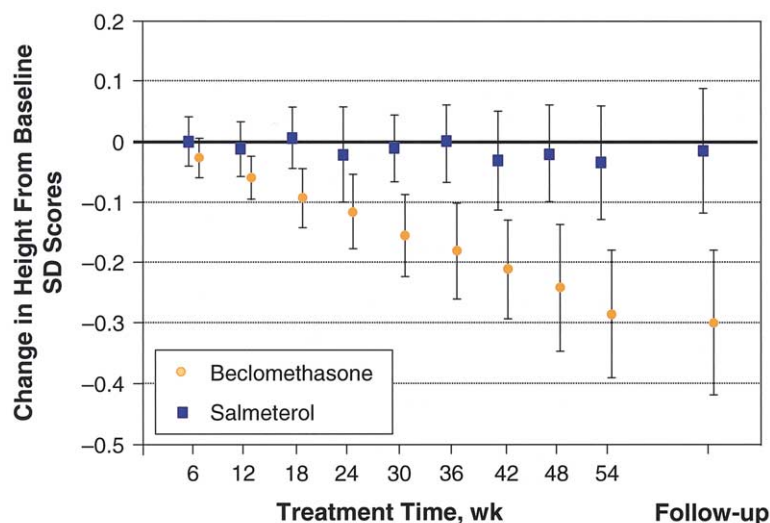


FIG 22. Effects of beclomethasone dipropionate and salmeterol on rate of growth. *SD*, Standard deviation. *Squares* and *circles* represent mean values for salmeterol and beclomethasone dipropionate, respectively, and *bars* represent the 95% CIs. Adapted from Verberne et al⁷⁵ and used with permission.

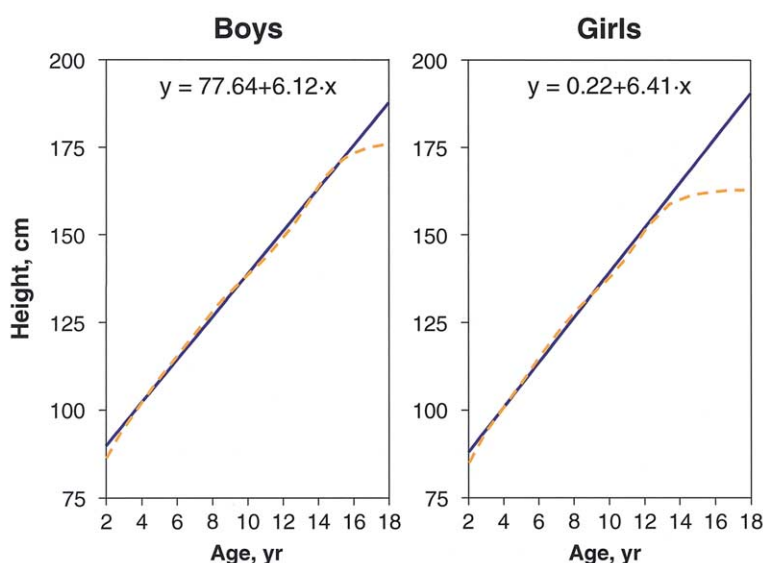


FIG 23. Relationship between height and age in boys and girls. *Dashed lines* represent the predicted normal height for age based on recently published Centers for Disease Control data.^{77,78} *Solid lines* represent the linear regression fit for the prepubertal for boys (2 to 12 years) and girls (2 to 11 years). The predicted prepubertal growth rate in boys is 6.12 cm/y (95% CI, 6.06-6.17 cm/y). The predicted prepubertal growth rate in girls is 6.41 cm/y (95% CI, 6.35-6.46 cm/y).

steroids. Because therapeutic and systemic effects vary, this comparison required a fundamental decision about whether to compare inhaled corticosteroids at doses that were equivalent with respect to therapeutic effect or equivalent with respect to systemic effects. The Dose of Inhaled Corticosteroids with Equisystemic Effects study was designed to characterize systemic effects of the

inhaled corticosteroids to determine “equisystemic” doses. The study used 6 inhaled corticosteroid preparations starting at a low dose and then doubling the dose at weekly intervals for a total of 4 doses.⁸³ This study found that the best outcome variable for assessing systemic effects was the area under the concentration-time curve for overnight hourly cortisol concentrations. By using this

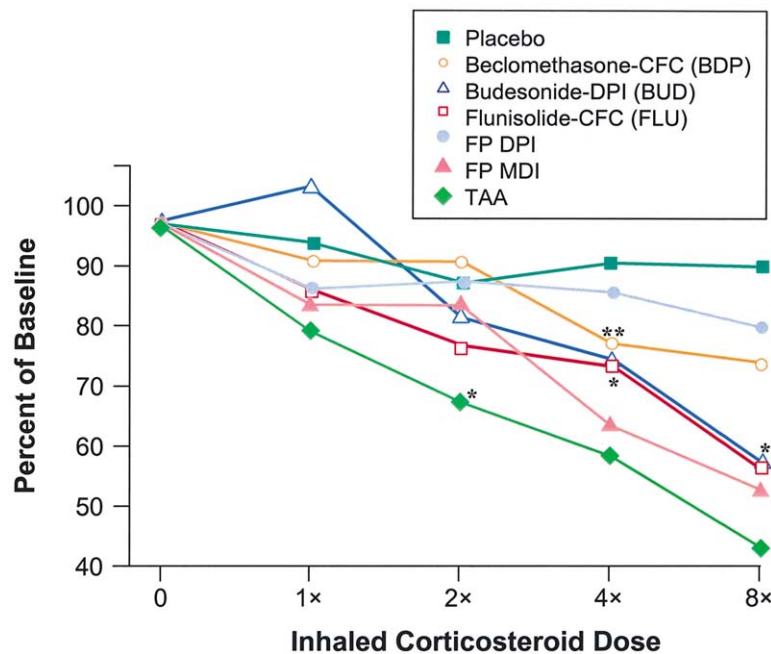


FIG 24. Geometric mean values for the plasma cortisol area under the concentration-time curve expressed as a percentage of the baseline control value for placebo, beclomethasone dipropionate (BDP), budesonide (BUD), flunisolide (FLU), fluticasone propionate via dry powder inhaler (FP DPI), fluticasone propionate via metered dose inhaler (FP MDI), and triamcinolone acetonide (TAA). Baseline data were determined, and low-dose corticosteroid was started on visit 3 followed by doubling of the inhaled corticosteroid dose on weekly visits thereafter. Total daily labeled dose at 1X, 2X, 4X, and 8X were as follows, respectively: BDP: 168, 336, 672, and 1344 μ g; BUD: 200, 400, 800, and 1600 μ g; FLU: 500, 1000, 2000, and 4000 μ g; FP DPI: 100, 200, 400, and 800 μ g; FP MDI: 88, 176, 352, and 704 μ g; and TAA: 800, 1600, 3200, and 6400 μ g. Adapted from Martin et al⁸³ and used with permission. *Highest recommended dose. **Highest recommended dose is 840 μ g.

measure, tremendous variations in systemic effect were detected that depended not only on the individual corticosteroid but also the delivery mechanism (Fig 24). Fluticasone propionate was minimally cortisol suppressive, even at high doses, when administered with a dry powder inhaler but very cortisol suppressive when administered by a metered dose inhaler. This study determined that an equivalent 10% cortisol suppression effect would be produced by 936 μ g of flunisolide (47% highest recommended dose [HRD]) via a chlorofluorocarbon metered dose inhaler, 787 μ g of triamcinolone acetonide (49% HRD) via a chlorofluorocarbon metered dose inhaler, 548 μ g of beclomethasone dipropionate (65% HRD) via a chlorofluorocarbon metered dose inhaler, 445 μ g of fluticasone propionate (22% HRD) via a dry powder inhaler, 268 μ g of budesonide (17% HRD) via a dry powder inhaler, or 111 μ g of fluticasone propionate (6% HRD) via a chlorofluorocarbon metered dose inhaler. The results suggest that flunisolide via a chlorofluorocarbon metered dose inhaler, triamcinolone acetonide via a chlorofluorocarbon metered dose inhaler, and beclomethasone dipropionate via a metered dose inhaler have a relatively wide safety margin with regard to cortisol suppression if administered within the recommended dosing limits.

Dose response of inhaled corticosteroids

Having determined equisystemic doses, ACRN evaluated comparative efficacy.⁸⁴ Beclomethasone dipropionate and fluticasone propionate, both administered with a chlorofluorocarbon metered dose inhaler, were chosen for this evaluation to permit assessments at comparable low (less than 5%), medium (20% to 30%), and high (40% to 60%) cortisol suppression doses. After subjects were randomized to receive one of the corticosteroids and followed for 3 consecutive 6-week intervals at progressively increasing doses, there was a single 3-week interval in which maximum efficacy response was determined for subjects by administration of 2000 μ g/day of fluticasone propionate by dry powder inhaler. FEV₁ response was seen with low-dose fluticasone propionate and medium-dose beclomethasone dipropionate (Fig 25). Similar results were seen with respect to methacholine responsiveness. Beyond this level, subsequent increases in dose produced only greater dose-dependent cortisol suppression, decreasing the therapeutic index, although marked intersubject variability was present. These data indicate that with respect to inhaled corticosteroids, most if not all of the clinical benefits occur at a low dose with minimal

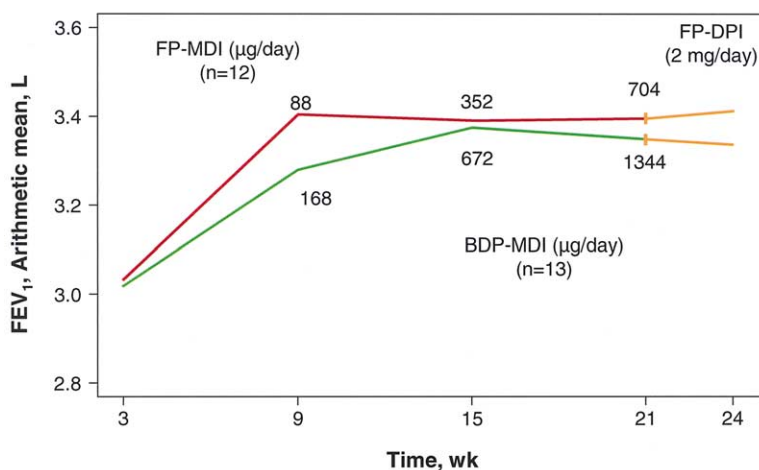


FIG 25. Arithmetic mean values for FEV₁ for fluticasone propionate via a metered dose inhaler (FP-MDI) and a dry powder inhaler (DPI) and beclomethasone dipropionate via a metered dose inhaler (BDP-MDI). Values above and below the line represent the dose in µg/day with doses chosen to represent low, medium, and high levels of cortisol suppression for the 2 metered dose inhaler preparations. Adapted from Szefer et al⁸⁴ and used with permission.

or no subsequent dose response. However, certain patients might require higher doses for clinical management, for example, for the prevention of significant exacerbations. In contrast, there is a clear dose-response curve with respect to systemic toxicity. Therefore, limiting exposure to the minimal effective dose maximizes the therapeutic index and decreases the risk of systemic adverse events.

Recommendation for the use of inhaled corticosteroids in growing children

In summary, several recommendations can be made with respect to the use of inhaled corticosteroids in growing children. The severity of the disease should be reduced as much as possible by implementing good environmental control to reduce allergens and their resultant airway inflammation. If inhaled corticosteroids are necessary, those with low oral bioavailability should be used at the lowest dose necessary to control symptoms. Because adverse events increase with dose and efficacy appears to peak at low to moderate doses, if symptoms cannot be controlled on a low to medium dose of inhaled corticosteroids, consideration should be given to supplementing the corticosteroid with a noncorticosteroid medication such as a long-acting β_2 -adrenergic agonist or alternatively a leukotriene receptor antagonist, rather than further increasing the corticosteroid dose to the high range. In addition, readily available measures of adverse effects such as growth parameters should be continuously monitored, especially in at-risk populations.⁸⁵ Additionally, it is important to continue to develop better methods to monitor overall asthma control, including signs of persistent inflammation, to be better able to monitor and titrate inhaled corticosteroids to their lowest effective dose. Finally, additional studies need to be performed to assess the effects of

inhaled corticosteroids on growing children. One significant limitation of the current data set is that efficacy studies tend to evaluate high doses of inhaled corticosteroids, whereas the systemic safety studies tend to evaluate low doses. Systemic effects and safety need to be better evaluated at corticosteroid doses consistent with those typically used in the clinical setting. Although knemometry might provide some preliminary information in this regard, ultimately this assessment will require long-term studies evaluating growth velocities and final adult heights.

EFFECTS OF CORTICOSTEROIDS ON THE EYE

Corticosteroids and the eye

Only very limited data are available on the ocular effects of inhaled corticosteroids. Furthermore, confounding variables make even these limited data difficult to interpret. For example, in the CAMP study, one child receiving budesonide developed a barely measurable (less than 0.5 mm) posterior subcapsular cataract.³² However, this child also received both oral prednisone and an intranasal corticosteroid. Data from studies evaluating the ocular effects of other forms of corticosteroids, however, can help in evaluating the potential for ocular complications with inhaled corticosteroids. These data, when combined with the available limited data, suggest that inhaled corticosteroids might produce significant adverse ocular effects. This potential complication cannot be ignored and should be better evaluated in future studies.

Corticosteroids can reach the eye by several routes of administration. Regardless of whether they were initially given intravenously, orally, or inhaled via the nose or

lungs, corticosteroids ultimately enter the systemic circulation. Similarly, when corticosteroid creams, lotions, and ointments are applied to the skin or when corticosteroid-containing otic drops are instilled into the ear, transdermal absorption occurs. Finally, in either solution or suspension, corticosteroids can be applied directly to ocular tissues. Similar to previous discussions, differences in potency, dose, preparation, and mode of administration of the various corticosteroid treatments can have significant ocular effects in response to these treatments.

In evaluating the ocular effect of corticosteroids, it is important to remember that, in contrast to bone, the eye is a very complex structure made up of many components, including the cornea, lens, ciliary bodies, vitreous cavity, and retina, with diverse structures and functions. The differences these components have in vascular and immunologic properties (eg, the cornea is avascular) could significantly affect their sensitivity to systemic corticosteroids. In addition, the components differ with respect to the density and distribution of corticosteroid receptors, further affecting their individual sensitivities to corticosteroids.⁸⁶ Moreover, adverse ocular effects might not even depend on specific corticosteroid receptors. Although the lens is one of the components adversely affected by corticosteroids, within the limits of detection it does not contain corticosteroid receptors.⁸⁷ Instead, corticosteroids bind to alpha crystallin in the lens in a nonspecific and nonfunctional manner that appears to be related to unique structural characteristics of this high molecular weight protein.⁸⁸ Furthermore, it is important to remember that in addition to their adverse ocular effects, corticosteroids have many beneficial effects on the various components of the eye and are used to treat a wide variety of ocular disorders.⁵⁸

Adverse effects of corticosteroids on the eye

There are many adverse ocular effects of corticosteroids. These include impaired wound healing, increased susceptibility to infection, and rare complications such as mydriasis, ptosis, myopia, pseudotumor cerebri, and exophthalmos. The principal and most common adverse ocular effects, however, are glaucoma and cataracts.

Glaucoma. Glaucoma is a characteristic effect of steroids on intraocular pressure, leading to optic neuropathy. It affects more than 3 million Americans, and overall it is the second leading cause of blindness in the elderly in the United States, ranking behind neovascularization due to diabetes. However, there are significant racial and ethnic differences. In the United States, glaucoma is 5 times more prevalent in black than white individuals and the leading cause of blindness in black Americans.⁸⁹ Although 30% of patients with glaucoma have a normal intraocular pressure (9 to 21 mm Hg), glaucoma typically occurs as a long-term consequence of an elevated intraocular pressure. Aqueous fluid is produced by the ciliary body in the eye, and approximately 90% of this fluid is removed from the anterior chamber via drainage through

the trabecular meshwork at the angles of Schlemm. When this drainage is reduced for whatever reason, intraocular pressure rises. Initially, this rise in intraocular pressure produces no symptoms. However, gradually over time, it leads to the signs and symptoms of glaucoma, namely an enlarged, edematous, and cloudy cornea; photophobia; tearing; blepharospasm; and field defects.

Secondary open-angle glaucoma has been a known complication of corticosteroid use since the 1950s. Multiple studies have demonstrated that overuse of exogenous corticosteroids leads to an increase in intraocular pressure with subsequent cupping of the optic disk, atrophy of the optic nerve, and the characteristic visual field defects. These changes occur because of compression of the globe of the eye and intraocular contents. Like the brain, the eye has a fixed, limited amount of space. When the fluid content within this space is increased because of limitations in the normal drainage mechanism, pressure rises. This leads to attempted decompression through the pathway of least resistance, the optic nerve, producing cupping of the optic disc. As with any other nerve, pressure on the optic nerve over time causes death of the nerve. In addition, the increase in intraocular pressure decreases vascular perfusion within the eye, producing ischemic damage. A similar ischemic optic neuropathy as a result of decreased perfusion is the mechanism by which temporal arteritis produces vision loss. Finally, exogenous corticosteroids exacerbate other forms of both normal and high-tension glaucoma.

Despite limited data, corticosteroid-induced glaucoma appears to be specific for exogenous corticosteroids.⁹⁰ In a study of 15 subjects with hypothalamic-pituitary Cushing syndrome due to an ACTH-producing tumor of the pituitary gland, only one subject had elevated intraocular pressure (23 mm Hg), and no subject had changes typical of glaucoma on photography of the retinal nerve fiber layer, morphometry of 15-degree color stereo optic disc diapositives, or perimetry.⁹¹

Ocular hypertension after exogenous corticosteroid administration depends on multiple factors including the drug, dose, frequency of administration, and corticosteroid responsiveness of the individual.⁹⁰ Within 2 to 4 weeks of starting corticosteroid therapy, approximately 5% of the population will start to increase their intraocular pressure.⁹² Ultimately, 18% to 36% of the population will respond to corticosteroid therapy with at least a moderate (5 mm Hg or greater) increase in intraocular pressure.⁹⁰ Moreover, several factors increase the risk of corticosteroid responsiveness. The prevalence of corticosteroid responsiveness increases to 46% to 92% in patients with primary open-angle glaucoma. In addition, patients older than age 40 years, patients with a family history of primary open-angle glaucoma, or patients with certain systemic diseases such as diabetes mellitus or high myopia are also more vulnerable to the effects of corticosteroids. Finally, although not fully established, an increase in corticosteroid responsiveness is also likely to occur in patients with other risk factors for glaucoma including race, hypertension, migraine headaches, and vasospastic disorders.⁹⁰

TABLE II. Glaucoma-producing effects of corticosteroids

Accumulation of extracellular matrix
Glycosaminoglycans
Fibronectin, elastin, laminin
Collagen types I and IV
Decreased enzyme synthesis
Tissue plasminogen activator
Collagenase
Stromelysin
Decreased phagocytic activity and reorganization of cytoskeletal elements
Enlargement of trabecular cells and nuclei and formation of cytoplasmic vesicles
Overexpression of myocilin (trabecular meshwork-induced glucocorticoid response protein), a sialoglycoprotein transcribed by the GLC1A gene
Other mechanisms
Prostaglandins E ₂ and F ₂ α
Abnormalities in corticosteroid metabolism

The pathogenesis of corticosteroid responsiveness is multifactorial (Table II). Steroids lead to an accumulation of glycosaminoglycans, fibronectin, elastin, laminin, and collagen types I and IV.⁹⁰ The accumulation of these substances in the extracellular matrix obstructs the flow of aqueous fluid through the outflow tract. Corticosteroids decrease the synthesis of various enzymes such as tissue plasminogen activator, collagenase, and stromelysin,⁹⁰ which would otherwise help remove outflow obstructions. Corticosteroids also decrease phagocytic activity and cause reorganization of cytoskeletal elements to decrease aqueous humor outflow.⁹⁰ In addition, they produce various histologic changes in the eye, including enlargement of trabecular cells and nuclei and the formation of cytoplasmic vesicles.⁹⁰ Corticosteroids cause the overexpression of myocilin, a sialoglycoprotein transcribed by the GLC1A gene, which was originally called the trabecular meshwork-induced glucocorticoid response protein.^{90,93} Numerous mutations in this gene have been identified in patients with glaucoma.⁹⁰ Intracocularly, corticosteroids decrease the expression of prostaglandin-synthesizing cyclooxygenase enzymes, reducing the production of both prostaglandin E₂ and F₂α.^{90,94} The importance of these prostaglandins in the pathogenesis of corticosteroid-induced glaucoma was established when synthetic prostaglandin analogs were shown to be effective in reducing intraocular pressure in these patients.⁹⁵ Finally, corticosteroid-responsive patients are more likely to have abnormalities in corticosteroid metabolism.⁹⁰

Corticosteroid-induced glaucoma is a problem in children as well as adults. In a study of children (mean age, 13.7 years) receiving daily oral prednisone for inflammatory bowel disease (mean duration of corticosteroid therapy, 2.4 years), 36% of the subjects (21 of 58) were characterized as intraocular pressure ("corticosteroid") responders, defined as an intraocular pressure of at least

20 mm Hg, at least a 6-mm Hg change in intraocular pressure between visits, or a minimum 6-mm Hg difference in intraocular pressure between the 2 eyes.⁹⁶ Elevated intraocular pressure correlated with the average daily prednisone dose during the 30-day period before the ocular examination.⁹⁶ Furthermore, 57% of corticosteroid responders (12 of 21) had a reduction in their intraocular pressure to within 2 standard deviations of control when the prednisone dose was reduced to less than 10 mg/day.⁹⁶ With respect to inhaled corticosteroids for asthma, Duh et al⁹⁷ reviewed the intraocular pressure data from more than 1000 subjects randomized to receive either inhaled budesonide or placebo in 4 studies. These studies accounted for the confounding effects of gender, race, age, history of diabetes, history of hypertension, clinical trial, systemic corticosteroid use during the trial, ophthalmic corticosteroid use during the trial, and prior oral corticosteroid use and found that, compared with control, total daily doses of budesonide ranging from 200 to 1600 µg for durations of 12 to 20 weeks did not produce significant elevations in intraocular pressure.⁹⁷ However, the published article did not provide enough supporting data to analyze these results. Furthermore, inhaled budesonide permitted a reduction in the exposure to oral prednisone,⁹⁷ and the lack of observed effect on intraocular pressure might be the result of simply substituting one corticosteroid for another. In a subset of 50 subjects receiving the highest budesonide dose, the mean change in intraocular pressure was 0.34 mm Hg ($P = .36$) compared with a mean change of 0.46 mm Hg ($P = .001$) for an average 10-mg prednisone dose during the 20-week study period.⁹⁷ This increase in intraocular pressure with inhaled corticosteroid might well have been statistically significant if more subjects had been available for analysis in this subset. Furthermore, the 12- to 20-week durations of treatment in the various components of this study might be inadequate to detect significant changes as a result of inhaled corticosteroids.

Studies of subjects receiving topical corticosteroids for other nonasthmatic conditions are less reassuring about the safety of these agents. Both ocular hypertension and glaucoma have been associated with the use of topical corticosteroids for eczema^{98,99} and vernal keratoconjunctivitis, a chronic inflammatory disease typically seen in the Mediterranean basin.¹⁰⁰

Cataracts. Cataracts are the second major adverse ocular effect of corticosteroids. They typically take months to years to develop and thus require long-term assessments to evaluate corticosteroid effect. Of the several different types of cataracts, one type is classically related to corticosteroids. Most cataracts are related to aging, with more than 50% of cataracts occurring in individuals older than age 65 years. Congenital cataracts develop before or shortly after birth. These cataracts are often bilateral and reflect a defect in the lens itself that might or might not affect vision. Cataracts that develop as a result of blunt or penetrating ocular trauma can present either shortly after the trauma or not until many years later. Finally, diseases such as diabetes and drugs

such as corticosteroids can produce secondary cataracts; these cataracts are posterior and subcapsular.

Similar to what is seen with intraocular pressure, the effect of corticosteroids on the development of cataracts appears to be specific for exogenous corticosteroids. Bouzas et al¹⁰¹ evaluated 60 consecutive subjects, 8 to 67 years of age, with endogenous Cushing syndrome. The mean duration of Cushing syndrome was 5.5 years (range, 1 to 20 years), and the mean urinary free cortisol excretion was 693 $\mu\text{g/day}$ (range, 250 to 3065 $\mu\text{g/day}$; normal values, 20 to 90 $\mu\text{g/day}$). Despite this, posterior subcapsular cataracts were detected in only 2 subjects (3.3%), and diabetes was a confounder in both of these subjects.

This low prevalence is in contrast to the high prevalence of cataracts seen with exogenous corticosteroids. The reason for this difference is as yet unknown. In the previously discussed study of ocular effects of prednisone in children with inflammatory bowel disease, posterior subcapsular cataracts were found in 12 of 58 subjects (20.7%) and no effects were noted in the control subjects.⁹⁶ Furthermore, 2 of these subjects had regression of their cataracts when the prednisone dose was reduced to less than 10 mg/day, indicating that cataracts as a result of corticosteroid use might, but do not necessarily, regress when the corticosteroid therapy is reduced or discontinued. Overall, 52% of the subjects who received corticosteroids in this study had an elevated intraocular pressure or a posterior subcapsular cataract.

Amemiya et al¹⁰² evaluated 44 subjects with generalized skin lesions due to atopic dermatitis who presumably had received or were currently receiving corticosteroids. Cataracts were detected in 25% of these subjects; 50% of the cataracts were the typical posterior subcapsular type that occurs with corticosteroids, 25% were the typical anterior type that occurs with atopic dermatitis, and 12.5% were a mixture of these 2 types. After acute exacerbations of dermatitis, the cataracts in 2 of these subjects progressed rapidly to total lens opacity during the course of 2 to 3 weeks, necessitating surgery. Of note, the clinical features of the subjects with cataracts did not appear to differ from those of subjects without cataracts, suggesting that the development of cataracts in this population might be dependent on other factors such as genetics.

With respect to inhaled corticosteroids, Toogood et al¹⁰³ performed a cross-sectional study in 48 adults with asthma. The mean duration of inhaled corticosteroid use was 9.2 years (range, 0.01 to 21 years), with a mean current dose of 1.5 mg/day (range, 0 to 3.2 mg/day). All but one of these subjects had also used or was using prednisone. The mean duration of prednisone therapy was 9.1 years (range, 0 to 29.8 years), with a mean current dose of 1.3 mg/day (range, 0 to 17.5 mg/day). Posterior subcapsular cataracts were found in 27% of the subjects, with the occurrence of cataracts correlating with the current daily dose and duration of prednisone therapy but not the dose or duration of inhaled corticosteroid therapy. This study concluded that although the results did not

exclude the possibility that inhaled corticosteroids might lead to cataracts, especially in subjects with high inherent susceptibility, the risk was negligible in the asthmatic population at large.

At approximately the same time, Simons et al¹⁰⁴ performed a cross-sectional study on 95 consecutive young subjects (median age, 13.8 years; range, 5.8 to 24.8 years) taking inhaled beclomethasone dipropionate or budesonide. The median duration of inhaled corticosteroid therapy was 5 years (range, 1 to 15 years), and the median dose was 750 $\mu\text{g/day}$ (range, 300 to 2000 $\mu\text{g/day}$) or 12.9 $\mu\text{g/kg/day}$. Information about lifetime exposure was not provided, but 77% of the subjects had not used oral corticosteroids within the preceding year. Although one of the subjects had a congenital cataract identified 10 years earlier, none of the subjects had a posterior subcapsular cataract, leading the authors to conclude that routine cataract screening was not warranted in this population.

In another study, Abuekteish et al¹⁰⁵ evaluated 140 children and young adults for posterior subcapsular cataracts. All subjects were receiving inhaled corticosteroids; in addition, 103 received short (7 days or less) courses of oral corticosteroids, and 4 had received prolonged (4 weeks or longer) courses of alternate-day oral corticosteroids. Bilateral posterior subcapsular cataracts were identified in one subject who had previously received a prolonged course of oral corticosteroids; no other cataracts were detected. The authors concluded that there was no evidence that inhaled corticosteroids, either alone or in association with short courses of oral corticosteroids, caused cataracts and that routine screening in these patients was unnecessary.

However, there are several problems with these studies. Many of the subjects evaluated were children or young adults. Because cataracts are age related and extremely rare in children, even large increases in relative risk could have been easily missed in these evaluations.¹⁰⁶ Furthermore, many of these subjects had also used oral corticosteroids, making it difficult to separate the effects of inhaled corticosteroids from the known effects of oral corticosteroids.¹⁰⁶ In contrast, Garbe et al¹⁰⁷ performed a case-control study of subjects 70 years of age or older enrolled in the Quebec universal health insurance program for the elderly. In this population there were 3677 subjects who underwent cataract extraction between 1992 and 1994. These subjects were compared with 21,868 randomly selected matched control subjects. After excluding subjects who had received systemic corticosteroids and adjusting for age, gender, diabetes, systemic hypertension, glaucoma, ophthalmic corticosteroids, and the number of physician claims for service, the use of inhaled corticosteroids for 3 or more years was associated with a 3.06-fold increase in the risk of undergoing cataract extraction (95% CI, 1.53 to 6.13). Furthermore, this increase in risk was related to the average daily dose of inhaled corticosteroid. Subjects who averaged more than 1 mg/day of beclomethasone dipropionate or budesonide for 2 or more years had a 3.4-fold

TABLE III. Cutaneous complications of corticosteroids

Common	Uncommon
Cushing syndrome	Pustular acne
Typical habitus	Tinea incognito
Moon facies	Stevens-Johnson syndrome
Buffalo hump	Perioral dermatitis
Truncal obesity	
Hirsutism	
Cutaneous striae	
Ecchymoses	
Atrophy	
Striae	
Ecchymoses	
Changes in mechanical properties	

increase in risk (95% CI, 1.49 to 7.76) compared with only a 1.63-fold increase in risk (95% CI, 0.85 to 3.13) for subjects who averaged no more than 1 mg/day.

Similarly, Cumming et al¹⁰⁸ conducted a population-based cross-sectional study in Australia. Of the 3654 subjects between the ages of 49 and 97 years recruited for this study, 370 were past or current users of inhaled corticosteroids. After adjusting for age and gender, inhaled corticosteroid use increased the relative prevalence of posterior cataracts by 1.9-fold (95% CI, 1.3 to 2.8) and the relative prevalence of nuclear cataracts by 1.5-fold (95% CI, 1.2 to 1.9). The prevalence of cortical cataracts was not affected by inhaled corticosteroid use. The prevalence of posterior subcapsular cataracts correlated with the cumulative lifetime dose of beclomethasone dipropionate, with the highest prevalence (27%; 5.5-fold increase in relative prevalence) seen in those subjects whose lifetime exposure exceeded 2000 mg. These larger population-based studies demonstrate that the use of inhaled corticosteroids is associated with the development of posterior subcapsular cataracts.

Recommendations for the use of inhaled corticosteroids and the eye

These limited data suggest that the use of inhaled corticosteroids is associated with an increased risk of adverse ocular effects. This increase in risk appears to be related to both high-dose and long-term use of the inhaled corticosteroid, although what exactly high-dose or long-term mean in this regard is poorly defined at present. With respect to the various inhaled corticosteroids, beclomethasone dipropionate appears to have a higher association with ocular adverse effects, although this might be a result of it being more commonly used and evaluated and thus not a true difference. Similarly, the influence of different delivery systems on ocular complications is unknown. However, given the limited data suggesting a dose-related increase in risk, minimizing ocular adverse events requires inhaled corticosteroids to be used at the lowest possible doses and for the shortest possible duration necessary for effective asthma

control. In addition, further research is necessary to clarify both the exact risk of ocular adverse events with inhaled corticosteroids and the role of potential confounders such as age, diabetes, congenital cataracts, and ocular trauma.

CUTANEOUS COMPLICATIONS FROM LONG-TERM USE OF INHALED CORTICOSTEROIDS

Types of cutaneous lesions

Corticosteroids produce several different types of cutaneous lesions (Table III). Although some of these lesions are common, others are uncommon. Pustular acne, a condition common in teenagers and associated with increasing levels of sex hormones, is produced or exacerbated by corticosteroid use in some individuals. Tinea incognito is a rare condition that occurs when a topical corticosteroid cream is used inappropriately to treat a tinea dermatitis, allowing the infection/rash to slowly spread while obscuring the characteristics such that the rash is no longer recognized as a tinea infection.¹⁰⁹ Stevens-Johnson syndrome is a severe allergic reaction that typically occurs in association with certain drugs, particularly the sulfonamides, nonsteroidal anti-inflammatory agents, and anticonvulsants.¹¹⁰ Although corticosteroids can be used to treat patients with Stevens-Johnson syndrome, on rare occasions they can also produce the disorder.^{110,111} Similarly, low-potency topical corticosteroids can be used to treat perioral dermatitis, an uncommon idiosyncratic response to the use of exogenous substances on the face, including topical corticosteroids.¹¹² Although it is important to be aware of these complications of corticosteroid use, they are uncommon and will not be further addressed. Instead, the remainder of this section will focus on common cutaneous complications of corticosteroid therapy.

Cushing syndrome. Cushing syndrome has been previously discussed with respect to fracture rates and the potential differences in adverse ocular effects between the endogenous and exogenous forms. In addition to the previously discussed abnormalities, patients with Cushing syndrome, regardless of etiology, develop a typical habitus that includes moon facies, buffalo hump, and truncal obesity. They also have excessive hair growth leading to hirsutism and develop cutaneous striae and ecchymoses, both of which will be reviewed subsequently.

Atrophy. Atrophy is another important cutaneous complication of corticosteroids. Corticosteroids cause the skin to become thin, fragile, and transparent. Very early in the process there is evidence of epidermal thinning as a result of reduced mitotic activity of keratinocytes in the germinal layer and flattening of rete ridges. Within weeks of corticosteroid exposure, however, dermal thinning as a result of loss of ground substance and reduction in fibroblast size occurs (Fig 26).¹¹³ These changes might ultimately be reversed on discontinuation of the corticosteroid.¹¹⁴ In addition to epidermal and dermal thinning, corticosteroids stimulate human dermal

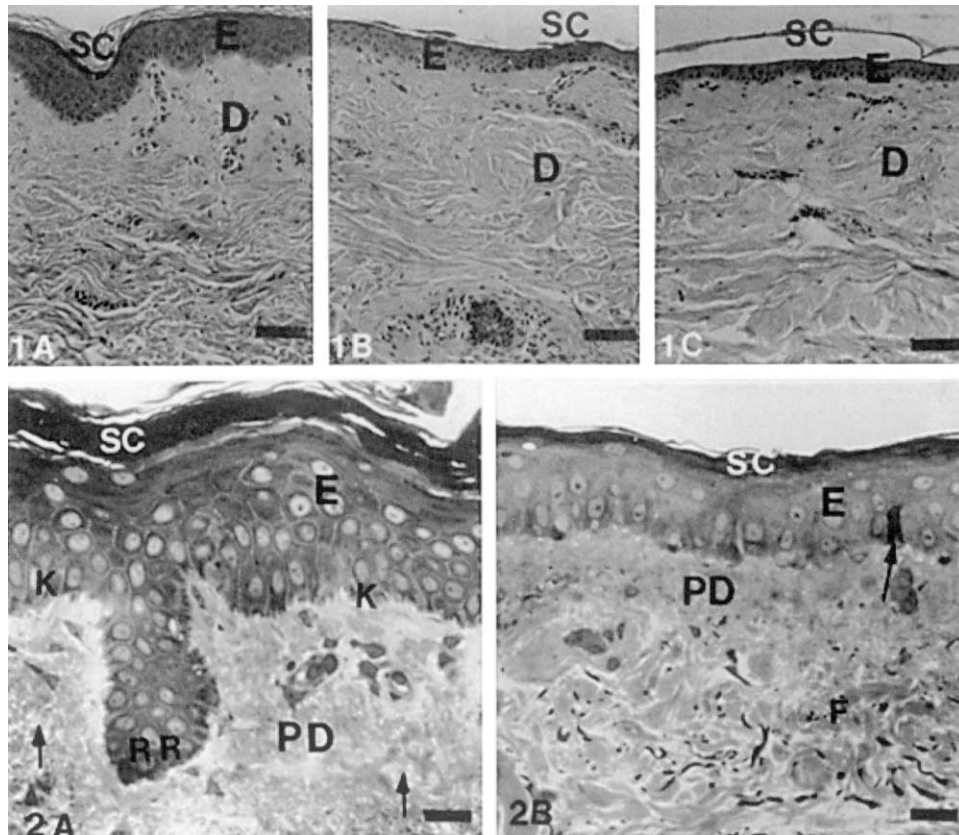


FIG 26. Thinning effect of topical corticosteroids on the dermis in normal human volunteers. The control state biopsy is shown at both low- (**1A**) and high- (**2A**) power magnifications. The biopsy sample taken after 3 weeks of exposure to a topical corticosteroid under an occlusive forearm dressing is shown at both low- (**1B**) and high- (**2B**) power magnification and **1C** shows the biopsy sample taken after 6 weeks of topical corticosteroid exposure at low-power magnification. After 3 weeks of topical corticosteroid exposure, there are substantial flattening and thinning of the epidermis (*E*), especially in the stratum corneum (*SC*) and the beginning of thinning of the dermis (*D*). These changes become more pronounced after 6 weeks of corticosteroid exposure with obvious thinning of the epidermis and dermis as well as disorganization of the collagen bundles within the dermis. High-power magnification clearly demonstrates loss of rete ridges (*RR*) and keratinocytes (*K*). *PD*, Papillary dermis. Arrows point to "lacy-like" arrangement of fibers in papillary dermis (**2A**) and focal areas of atypia in epidermis (**2B**). Adapted from Lehmann et al¹¹³ and used with permission.

microvascular endothelial cell development.¹¹⁵ Thus, atrophic skin changes as a result of corticosteroids frequently occur in association with the development of telangiectasias. This vascular development is important when considering the mechanism of action for the adverse cutaneous effects of inhaled or other corticosteroids not topically applied to the skin.¹¹⁶ Tachyphylaxis to these cutaneous effects of topical corticosteroids occurs occasionally, although the mechanism is unknown.^{117,118} In addition, early animal data suggested that all-*trans* retinoic acid could prevent corticosteroid-induced skin atrophy without compromising the anti-inflammatory properties of the corticosteroid.¹¹⁹ This effect, confirmed in both transplant recipients requiring long-term oral corticosteroids for immunosuppression¹²⁰ and psoriasis patients requiring topical corticosteroids,¹²¹ is probably the direct effect of all-*trans* retinoic acid on fibroblasts stimulating the production of ground substance.

Striae. Striae, another common complication of corticosteroid therapy, are visible linear scars that form in areas of dermal damage, presumably from mechanical stress. Striae develop in several steps. Initially, inflammation and edema develop within the dermis at areas of stress. Dermal collagen is then deposited layered in thin eosinophilic bundles oriented along the lines of mechanic stress. In addition, elastin fibers, oriented similar to the collagen bundles, become more numerous.¹²² Unlike dermal atrophy, striae are essentially scar tissue and, therefore once developed, are permanent and do not reverse on withdrawal of corticosteroid. The problem with using striae as a biomarker for the cutaneous corticosteroid complication is that they are not specific for this condition and frequently occur during the adolescent growth spurt and pregnancy, especially in body areas undergoing rapid increases in size. Thus, although striae have occasionally been reported with the use of inhaled corticosteroids, they are not particularly helpful as a biomarker.

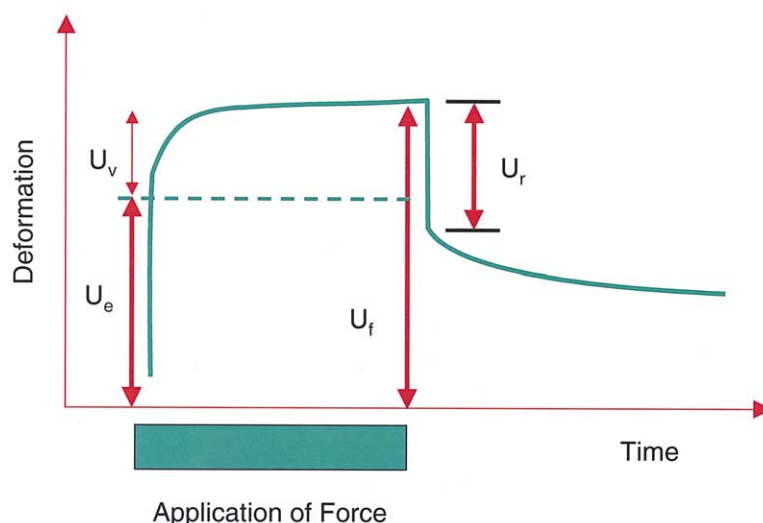


FIG 27. Deformation of the skin in response to the application of a distending force. Viscoelasticity with respect to immediate distention of the skin is defined as the ratio between the delayed distention (U_v) and the immediate distention (U_e), and biologic elasticity is defined as the ratio of the immediate retraction (U_r) and the final deformation (U_f) with U_f being the sum of U_e and U_v . Adapted from Kennedy¹²³ and used with permission.

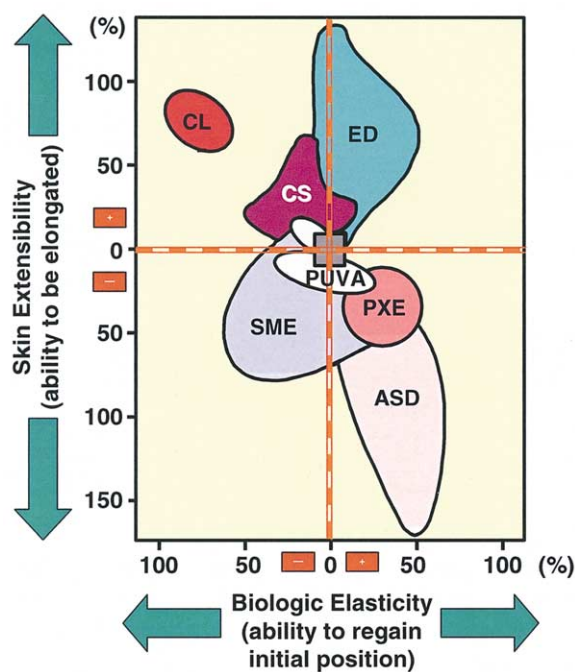


FIG 28. Relationship between skin extensibility and biologic elasticity in cutis laxa (CL), corticosteroid atrophy (CS), photosclerosis, and photoatrophy due to psoralen plus long wave ultraviolet radiation (PUVA), Ehlers-Danlos types I and II (ED), scleromyxedema (SME), acroscleroderma (ASD), and pseudoxanthoma elasticum (PXE). The zeros on the x and y axes represent normal, and the plus and minus signs indicate increases and decreases, respectively, in extensibility and elasticity. Reprinted from Kennedy¹²³ and used with permission.

Ecchymoses. Besides atrophy, the other common cutaneous complication that serves as a biomarker of a corticosteroid effect is ecchymoses. Ecchymoses are macular

areas of hemorrhage more than 2 mm in diameter that occur as a result of loss of ground substance, lack of structural support for vessels, and dilation of vessels in the dermal layer. Similar to atrophy, ecchymoses are reversible on discontinuation of the corticosteroid. However, similar to striae, they are nonspecific and occur with a variety of biologic processes including trauma, thrombocytopenia, coagulopathy, and vessel abnormalities such as amyloidosis and scurvy.

Changes in skin extensibility and elasticity. Although rarely considered, changes in the mechanical properties of skin are common complications of corticosteroid therapy. These changes can be readily evaluated and are potential biomarkers of systemic corticosteroid effect. The skin has several quantifiable elastic properties. When force is applied to the skin, there is an immediate rapid distention, followed by a more gradual delayed distention that ultimately reaches a plateau called the final deformation. Similarly, when this force is removed, there is an immediate retraction of the skin followed by a more gradual retraction to a new plateau (Fig 27).¹²³ Each of these changes can be measured and used to determine extensibility and elastic properties of the skin such as viscoelasticity with respect to the immediate distention (the ratio of the delayed to the immediate distention) and biologic elasticity (the ratio of the immediate retraction to the final deformation, or total distention). The relationship between extensibility and elasticity of skin has been determined for a variety of disorders including corticosteroid atrophy, cutis laxa, Ehlers-Danlos types I and II, photosclerosis and photoatrophy, scleromyxedema, acroscleroderma, and pseudoxanthoma elasticum (Fig 28).¹²³ Changes in the mechanical properties of skin occur rapidly after administration of corticosteroid. In one study they were detected within 2 hours of intravenous infusion of prednisolone and persisted for at least

1 week.¹²⁴ The simple mechanical skin properties are reproducible, easy to measure in a nontoxic and noninvasive manner, and ideally suited to the serial evaluation of patients receiving corticosteroids.

Aging, sun, and sex hormones

It is sometimes difficult to distinguish the cutaneous effects of corticosteroids from those related to aging, sun exposure, and sex hormones. Aging produces dry, wrinkled, loose skin in women after age 35 years and men after age 45 years. Similar to the atrophy seen with corticosteroids, these changes result from a decreased skin thickness, especially in light-protected sites, a flattening of the dermal-epidermal junction, and a decrease in elastic recovery. Changes similar to those seen with aging occur as a result of sun exposure (photoaging), although these changes are seen in exposed rather than light-protected sites. Finally, premenopausal and postmenopausal hormonal changes significantly affected the extensibility and elasticity of skin in women.^{125,126} There is much overlap between the cutaneous effects of corticosteroids and those due to aging, sun exposure, and female sex hormones.

Mechanism of corticosteroid lesions

Most of the information on the mechanism of corticosteroid-induced skin changes comes from studies with topical corticosteroids. Topical corticosteroids clearly reduce mitotic activity in the epidermis. In addition, they directly reduce the synthesis of both collagen and glycosaminoglycans by fibroblasts in the dermis. These factors combine to produce a loss of the supporting matrix for the skin and ultimately skin atrophy. In addition to these atrophic effects, topical corticosteroids have pronounced vascular effects, including an initial vasoconstriction of superficial vessels followed by a fixed rebound vasodilation with continued applications. This combination, namely the loss of supporting matrix plus the fixed rebound vasodilation, predisposes the individual to ecchymoses. Although skin blanching as a result of the initial vasoconstriction of topical corticosteroids is a well-established means for assessing relative efficacy of various corticosteroid preparations, the exact cause of this vasoconstriction is still unknown.

Frequency of cutaneous corticosteroid complications

Hydrocortisone was first introduced in 1952. This drug has low potency and lacks topical activity. The adverse cutaneous effects of corticosteroids became apparent much later, only as more potent and topically active drugs were developed. Inhaled corticosteroids were introduced in the 1960s, but their adverse cutaneous effects were not recognized until the late 1980s. Oral corticosteroids have a high prevalence of cutaneous adverse effects. In a review, McEvoy and Niewoehner¹²⁷ reported that systemic corticosteroids produced 4-fold increases in the frequency of moon facies, buffalo hump, truncal obesity, acne, and hirsutism. Even with low-dose cortico-

steroid therapy (12 mg or less), moon facies occurred in 13% of subjects after at least 60 days of treatment and in up to 66% of subjects after more than 5 years of treatment. Finally, nearly 50% of the subjects receiving corticosteroids reported easy bruising compared with only 11% of control subjects.¹²⁷ Certainly the entire spectrum of moon facies, buffalo hump, truncal obesity, acne, and hirsutism are significantly more common with oral than with inhaled corticosteroids, and the fact that many users of inhaled corticosteroids also receive oral corticosteroids probably delays recognition of the subtler cutaneous effects of inhaled corticosteroids.

Probably the first study clearly identifying adverse cutaneous effects of inhaled corticosteroids was published in the *British Medical Journal* in 1990.¹²⁸ This study evaluated 68 subjects with asthma or chronic bronchitis who received a constant dose and regimen of inhaled or systemic therapy for at least 6 months. Fifteen subjects received long-term systemic corticosteroid therapy (prednisolone, 5 to 20 mg/day); 21 received high-dose inhaled corticosteroid therapy (beclomethasone dipropionate, 1000 to 2250 µg/day) and had never received long-term systemic corticosteroid therapy; 15 received low-dose inhaled corticosteroid therapy (beclomethasone dipropionate, 200 to 800 µg/day) and had never received either long-term systemic or high-dose inhaled corticosteroid therapy; and 17 were control subjects who had never received either inhaled or systemic corticosteroids. Skin thickness was measured at 3 sites by ultrasound and adjusted for gender, and purpura was clinically assessed by a dermatologist blinded to the subjects' disease and treatment. Compared with control subjects, skin thickness in millimeters was significantly ($P < .01$) reduced at all 3 sites by either oral or high-dose inhaled corticosteroids with a clear dose-response relationship (Fig 29, A). Similarly, there was a significant trend ($P < .01$) for increasing purpura with increasing corticosteroid exposure (Fig 29, B).

More recently, collagen synthesis in the skin was assessed in subjects after 6 weeks of treatment with either inhaled budesonide or nedocromil.¹²⁹ Both low-dose (400 µg/day) and high-dose (1600 µg/day) budesonide significantly decreased both types I and II procollagen propeptide concentrations in suction blisters compared with nedocromil control subjects, with no significant differences detected between the low- and high-dose groups. Similarly, Haapasaari et al¹³⁰ evaluated procollagen propeptide concentrations in suction blister fluid and skin thickness in 27 new asthmatic subjects on moderate doses of budesonide or beclomethasone dipropionate, 6 of whom had also received 1 or more courses of oral corticosteroids. Procollagen propeptide concentrations were markedly reduced after 3 and 6 months of inhaled corticosteroid therapy. Despite this, abdominal wall skin thickness was unchanged, and upper arm skin thickness was only minimally reduced after 1 to 2 years of inhaled corticosteroid therapy.

The risk of ecchymoses has also been evaluated. Mak et al¹³¹ used a questionnaire to determine the prevalence

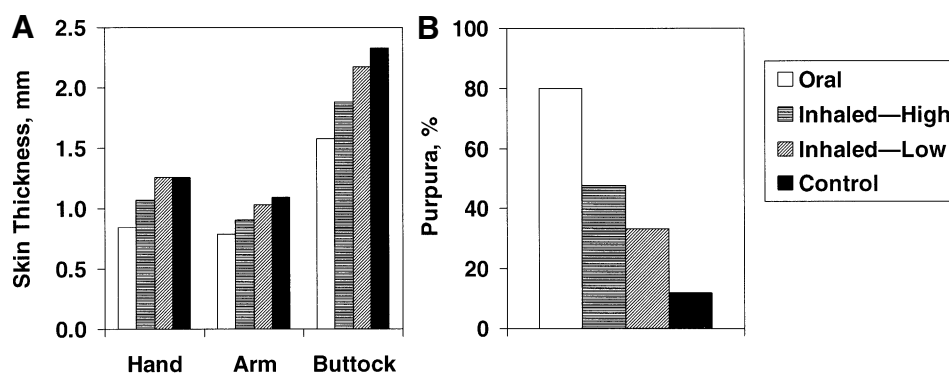


FIG 29. Effect of corticosteroids on skin thickness in millimeters (**A**) and the prevalence of purpura (**B**) in subjects with asthma and chronic bronchitis receiving at least 6 months of oral corticosteroids (prednisolone, 5-20 mg/day) [Oral]; high-dose inhaled corticosteroids (beclomethasone dipropionate, 1000-2250 µg/day) [Inhaled-High]; low-dose inhaled corticosteroids (beclomethasone dipropionate, 200-800 µg/day) [Inhaled-Low]; and controls (Control). Based on data from Capewell et al.¹²⁸

of easy bruising in 202 outpatients receiving inhaled corticosteroid through a respiratory clinic. The investigators compared their results to those obtained in 204 outpatients attending nonrespiratory clinics who were not receiving any corticosteroids. Age and gender distributions were similar between the 2 groups. Easy bruising was found in 47% of inhaled corticosteroid users compared with 22% of noncorticosteroid users (relative risk, 2.18; 95% CI, 1.62 to 2.94). Women had a significantly higher risk of bruising than men either with inhaled corticosteroids (relative risk, 1.59; 95% CI, 1.18 to 2.16) or without inhaled corticosteroids (relative risk, 6.04; 95% CI, 2.48 to 14.68). However, because of the low risk of bruising in men not receiving inhaled corticosteroids, men (relative risk, 5.80; 95% CI, 2.36 to 14.13) had a greater increase in relative risk because of inhaled corticosteroids than women (relative risk, 1.80; 95% CI, 1.32 to 2.44). As expected, the risk of bruising in users of inhaled corticosteroids increased with age, dose, and duration of therapy.

In a similar study, Roy et al¹³² evaluated skin bruising by both questionnaire and cutaneous examination and blood and urine cortisol levels. One hundred adults who had received high-dose budesonide or beclomethasone dipropionate for at least 3 months were compared with 100 age- and gender-matched control subjects from an ophthalmology outpatient clinic. There was a significant ($P < .001$) association between skin bruising as reported on the questionnaire and direct examination and by multiple logistic regression. This bruising correlated both with female gender (odds ratio, 20; 95% CI, 13 to 33) and inhaled corticosteroid use (odds ratio, 12; 95% CI, 8 to 18). Similar to the study by Mak et al,¹³¹ among inhaled corticosteroid users, bruising significantly correlated with both age and female gender. Furthermore, bruising correlated with suppression of adrenal function; urinary cortisol levels were significantly lower in subjects reporting

skin bruising and decreased with increasing number of bruises detected on direct physical examination.

These studies clearly demonstrate that consistent with the findings using topical corticosteroids, inhaled corticosteroids have a significant adverse effect on skin. This adverse effect consists of a reduction in collagen synthesis, a reduction in the thickness of skin, and an increase in the risk of ecchymoses. Furthermore, these changes directly relate to systemic exposure as detected by changes in the HPA axis.

Cutaneous changes: Physician versus patient perspective

Physicians and patients differ greatly in their perception of the potential cutaneous complications of inhaled corticosteroid use. In a survey of 213 physicians specializing in the treatment of asthma (80% allergists/immunologists, 20% pulmonologists), skin changes were the second most frequently reported complication of inhaled corticosteroids; the most frequently reported complication was local oropharyngeal effects.¹³³ Overall, 6% of respondents reported that they frequently saw and 24% reported that they occasionally saw bruising and/or thin skin in patients receiving oral corticosteroids. Consistent with the previously discussed research studies, these skin changes were age related; 55% of the changes were seen in elderly patients, 33% in middle-aged patients, and only 10% in children. In contrast, a survey of 603 asthmatic patients showed that although 53% of the patients were very or somewhat concerned about using inhaled corticosteroids, principally because of concern over adverse events (59%), the potential adverse events that concerned respondents most were neither oral pharyngeal nor cutaneous. Instead, potential adverse events of greatest concern were weight gain (29%), building huge muscles (24%), infections (20%), brittle bones (16%), stunted growth (14%), cataracts (8%), and diabetes (7%). Presumably because of

TABLE IV. Cutaneous evaluation in studies of long-term inhaled corticosteroid use*

Study	n	Age (y)	Duration (y)	Cutaneous adverse events noted
Dompeling et al ¹³⁸	56	~50	2	0
Paggiaro et al ¹³⁹	281	50-75	0.5	0
Vestbo et al ¹⁴⁰	290	30-70	3	0
Burge et al ¹³⁶	751	40-75	3	Trend to more bruising
Lung Health Study ¹³⁷	1116	40-69	3.5-4.5	0
Childhood Asthma Management Program ³²	1041	5-12	4-6	0

*Methods used to assess cutaneous adverse events were not stated in the literature.

these fears, 46% of patients were reluctant to use inhaled corticosteroids on a regular basis.¹³⁴ If patient compliance and overall asthma control are to be improved, better patient education is clearly needed regarding the likely adverse events of inhaled corticosteroid use, the true risk and severity of these events, and how these compare with the risks of inadequately treated asthma.

Evaluation of cutaneous effects

The labeling of inhaled corticosteroids also contributes to the inappropriate perception regarding adverse skin events. For example, under adverse skin events occurring at a frequency of more than 1% and greater than placebo, the product information for fluticasone propionate lists rashes, urticaria, photodermatitis, dermatitis and dermatosis, viral skin infections, eczema, fungal skin infections, pruritus, acne, and folliculitis.²⁴ Similarly, the product information for beclomethasone dipropionate lists adverse events that occur in fewer than 2% of patients; in this category, listed under skin and appendages are rash, skin discoloration, and urticaria.¹³⁵ The labeling for neither fluticasone propionate nor beclomethasone dipropionate specifically lists atrophy or ecchymoses as adverse events. Although budesonide labeling does list ecchymosis under platelet, bleeding, and clotting disorders, it does not list skin atrophy or any other adverse skin events occurring at a frequency of more than 1% and at a greater rate than with placebo.²³

This lack of recognition of the cutaneous complications of inhaled corticosteroids appears to be a function of the way trials of these drugs have been designed and conducted during the past several years. Table IV^{32,136-140} summarizes several recently published clinical trials that evaluated the long-term use of inhaled corticosteroids. None of these studies listed any specific means of assessing subjects for cutaneous complications in their published methods. As a result, in 5 of the 6 studies involving almost 3000 subjects, no cutaneous adverse events were noted^{32,137-140}; in the remaining study, the only mention of cutaneous complications was a comment that there was a trend to more bruising in subjects receiving inhaled corticosteroids.¹³⁶ When an assessment of cutaneous complications is included in the study design, however, the results are markedly different. Pauwels et al¹⁴¹ evaluated

1277 subjects with chronic obstructive pulmonary disease randomized to receive twice daily budesonide (400 µg) or placebo. At each study visit, the subjects were examined, and skin bruises larger than 50 mm on the volar side of the forearms were noted. During the 3-year study period, 364 bruises were noted in the budesonide group compared with 42 in the placebo group ($P < .001$). The overall prevalence of bruising was 10% with budesonide and 4% with placebo ($P < .001$), and bruises were present on up to 4.9% of budesonide-treated subjects at any individual visit.¹⁴¹ Cutaneous events occur in a significant percentage of patients receiving inhaled corticosteroids. However, if their assessment is not included in the study design, it is highly unlikely that they will be detected and reported, furthering the misperceptions about this abnormality.

Although these cutaneous changes might not be clinically relevant with respect to continuation of inhaled corticosteroid therapy in a subject with persistent asthma or other chronic respiratory abnormalities, they are a good, easily obtained biomarker of systemic effects of corticosteroids. Future studies of inhaled corticosteroids should include a standardized skin examination for bruises. Although bruises are nonspecific, they are detected in a relatively easy to perform evaluation that can clearly show significant differences when incorporated into the study design. Ideally, the study design should also include assessment of dermal thickness by using high-frequency ultrasound. This assessment is extremely sensitive, easy to perform, and very reproducible, with a very small coefficient of variation.^{128,130}

Summary of cutaneous effects

Clearly, long-term use of inhaled corticosteroids produces cutaneous complications. Of these complications, skin thinning and bruising occur with sufficient frequency to be useful as biomarkers of systemic corticosteroid activity; other cutaneous complications are uncommon. Cutaneous complications are a function of corticosteroid dose, potency, and duration of use. Although they represent a systemic effect, their exact mechanism is unknown and is probably multifactorial, including direct inhibitory effects on keratinocytes in the epidermis and fibroblasts in the dermis as well as a variety of vascular effects. In some individuals, they might produce cosmet-

ic concerns, but generally they are not serious and the benefits of inhaled corticosteroids outweigh the cosmetic concerns. Thus, these complications do not usually require discontinuation of inhaled corticosteroid therapy.

CONCLUSION: HOW CLOSE ARE WE TO THE IDEAL CORTICOSTEROID?

We have come a long way since the introduction of hydrocortisone. Not only is persistent asthma now treated with extremely potent and effective corticosteroids, but also the therapeutic index of corticosteroids has been improved by the development of inhalation devices and techniques that permit direct delivery of these steroids to their site of action in the lungs, reducing systemic exposure. Despite these advances, adverse systemic effects still exist.

The use of corticosteroids leads to a decrease in mineralization in bone, increasing the risk of fractures. Although inhaled corticosteroids have a better safety profile with respect to this risk than oral corticosteroids, they still affect mineralization. This might be a cumulative dose effect, because it is dependent on both dose and duration of corticosteroid therapy, but it is not immutable. Data suggest that the various inhaled corticosteroid preparations have significant differences in the degree to which they affect mineralization, although the cause and exact extent of these differences are unknown. If the cause of these differences can be determined, it might be possible to use this information to develop inhaled corticosteroids that have minimal to no adverse effect on bone. In addition, because the currently available inhaled corticosteroids decrease bone mineralization, it is important to serially monitor this parameter in patients receiving inhaled corticosteroid therapy, especially at high doses, and to be prepared to intervene therapeutically whenever appropriate to reduce bone mineral loss, especially in at-risk individuals such as those with a family history of osteoporosis or at at-risk times such as around menopause.

Similarly, inhaled corticosteroids can reduce growth velocity in children, although this reduction is less than that seen with systemic corticosteroids. Response varies significantly; not all children receiving inhaled corticosteroids develop an abnormal growth velocity. Even when an abnormal growth velocity develops, it is usually temporary. Several studies have demonstrated that with long-term inhaled corticosteroid use, growth velocity returns to normal after 1 to 2 years. Furthermore, when considering the potential adverse effects of inhaled corticosteroids on growth, it is important to remember that asthma itself produces growth suppression. Thus, the beneficial effects on growth derived from successful treatment of asthma might outweigh any potential detrimental effect of the corticosteroid. In fact, several studies have found that final adult height was unaffected by inhaled corticosteroids despite an initially documented reduction in growth velocity.

Although only limited data are available, inhaled corticosteroids also appear to produce ocular complications, principally glaucoma and cataracts. The data suggest that there is a trend for increasing intraocular pressure with the

use of high-dose inhaled corticosteroids. Larger, adequately powered studies are likely to confirm this trend, especially given the fact that the limited systemic exposure received from topical corticosteroid in the treatment of eczema has been shown to produce glaucoma. Cataracts appear to be the one adverse systemic effect of corticosteroids that is not dependent on the corticosteroid receptor. Instead, cataracts appear to depend on the nonspecific binding of corticosteroids to high molecular weight proteins in the eye. With the exception of the congenital variety, cataracts take time to develop and are rare in children and young adults. Perhaps because of this, studies performed in these patient groups have failed to demonstrate any association between inhaled corticosteroids and the development of cataracts. Studies conducted in middle-aged and elderly individuals, however, demonstrate that inhaled corticosteroid use clearly increases the risk of cataracts by 2- to 3-fold. Similar to the effects on bone, this increase in risk is directly related to cumulative lifetime exposure as determined by the average daily dose and duration of therapy.

Finally, topical and oral corticosteroids significantly affect the growth and development of skin. Although clinical trials have rarely evaluated the cutaneous effects of inhaled corticosteroids, the available data confirm that inhaled corticosteroids also produce these effects. These cutaneous effects typically are not severe and do not require any alteration in corticosteroid therapy. However, because they are a function of dose, potency, and duration of inhaled corticosteroid use and because 2 of these effects, namely skin atrophy and ecchymoses, are simple, reproducible parameters that can be determined safely and noninvasively, these cutaneous changes might prove to be useful biomarkers of systemic corticosteroid activity.

The ideal inhaled corticosteroid should have a high local activity in the lung with minimal to no systemic adverse events. Such a corticosteroid would have a long residence time in the lung, either as a result of being trapped in the lung through the formation of lipid conjugates or as the result of very slow diffusion properties. In addition, to minimize the effect of the corticosteroid once it diffuses out of the lung, the ideal corticosteroid should have high protein binding and high systemic clearance, minimizing its chance to interact with extrapulmonary corticosteroid receptors. It should have low oral bioavailability, minimizing the effects of any swallowed portion of the delivered dose. Finally, it should be a prodrug that is locally activated in the lungs, reducing the potential for adverse oropharyngeal effects such as pharyngitis and candidiasis.

This ideal corticosteroid will probably never be developed because it appears that the same receptor is responsible for corticosteroid efficacy in the lung and adverse systemic effects. Furthermore, this receptor is intracellular. Because any efficacious corticosteroid has to be able to cross cell membranes to interact with this receptor, it is impossible to totally prevent diffusion from the lungs into the systemic circulation. Thus, it is not feasible to create a drug that is efficacious in the lung and yet does not cause some physiologic perturbation at receptor sites outside the lung.

These nonefficacious perturbations must be kept in perspective, however. Asthma is a disease that produces significant morbidity and mortality, and the benefits of inhaled corticosteroid therapy in this disease are well established and far in excess of any systemic adverse effects. Furthermore, even in the absence of the ideal corticosteroid, these systemic adverse effects can be reduced. Data indicate that the efficacy of currently available inhaled corticosteroids might plateau at low to moderate doses with higher doses producing no further improvement. On the other hand, systemic adverse effects do tend to increase with dose. Thus, adverse effects can be minimized by using the lowest possible effective dose to maintain therapeutic efficacy. In addition, when therapeutic efficacy cannot be maintained on a low to moderate dose of inhaled corticosteroid, consideration should be given to supplementing the corticosteroid with another noncorticosteroid medication rather than simply increasing the corticosteroid dose. Finally, efforts should continue in the development of new corticosteroids that are closer to the ideal corticosteroid than currently available agents. These new corticosteroids should maximally incorporate as many of the properties of the ideal corticosteroid as possible, thus improving the therapeutic index and further reducing adverse systemic effects relative to the currently available compounds.

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