Systemic Adverse Effects of Inhaled Corticosteroid Therapy

A Systematic Review and Meta-analysis

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Objective: To appraise the data on systemic adverse effects of inhaled corticosteroids.

Methods: A computerized database search from January 1, 1966, through July 31, 1998, using MEDLINE, EMBASE, and BIDS and using appropriate indexed terms. Reports dealing with the systemic effects of inhaled corticosteroids on adrenal gland, growth, bone, skin, and eye, and reports on pharmacology and pharmacokinetics were reviewed where appropriate. Studies were included that contained evaluable data on systemic effects in healthy volunteers as well as in asthmatic children and adults. A statistical meta-analysis using regression was performed for parameters of adrenal suppression in 27 studies.

Results: Marked adrenal suppression occurs with high doses of inhaled corticosteroid above 1.5 mg/d (0.75 mg/d for fluticasone propionate), although there is a considerable degree of interindividual susceptibility. Meta-analysis showed significantly greater potency for dose-related adrenal suppression with fluticasone compared with beclomethasone dipropionate, budesonide, or triamcinolone acetonide, whereas prednisolone and fluticasone propionate were approximately equivalent on a 10:1-mg basis. Inhaled corticosteroids in doses above 1.5 mg/d (0.75 mg/d for fluticasone propionate) may be associated with a significant reduction in bone density, although the risk for osteoporosis may be obviated by postmenopausal estrogen replacement therapy. Although medium-term growth studies showed suppressive effects with 400-µg/d beclomethasone dipropionate, there was no evidence to support any significant effects on final adult height. Long-term, high-dose inhaled corticosteroid exposure increases the risk for posterior subcapsular cataracts, and, to a much lesser degree, the risk for ocular hypertension and glaucoma. Skin bruising is most likely to occur with high-dose exposure, which correlates with the degree of adrenal suppression.

Conclusions: All inhaled corticosteroids exhibit dose-related systemic adverse effects, although these are less than with a comparable dose of oral corticosteroids. Meta-analysis shows that fluticasone propionate exhibits greater dose-related systemic bioactivity compared with other available inhaled corticosteroids, particularly at doses above 0.8 mg/d. The long-term systemic burden will be minimized by always trying to achieve the lowest possible maintenance dose that is associated with optimal asthmatic control and quality of life.

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The last decade has led to a greater understanding of the mechanisms causing asthma and particularly the underlying role of the inflammatory process in this condition. Corticosteroids are generally accepted to be the first-line choice of anti-inflammatory therapy for the treatment of asthma. The delivery of topically active corticosteroids directly to the airways by inhalation has revolutionized the anti-inflammatory treatment of asthma. As a consequence, it is now relatively uncommon to see the unpleasant systemic adverse effects that are associated with oral corticosteroid maintenance therapy.

Present asthma management guidelines emphasize the importance of early intervention with inhaled corticosteroids as first-line anti-inflammatory therapy. There has been a trend toward the use of higher doses, which seems contrary to most of the available evidence of the dose-response relationships for efficacy of inhaled corticosteroids in asthma. Against this background, there has been increasing awareness that inhaled corticosteroids are associated with dose-related systemic adverse effects. This in turn has resulted in debate regarding the relative risks and benefits of newer vs older inhaled corticosteroids. At the same time, there has been increasing awareness that adding long-acting β2-agonists, theoph-
MATERIALS AND METHODS

The literature was searched for 30 key terms from January 1, 1966, through July 31, 1998, using the the databases of MEDLINE (National Library of Medicine), EMBASE (Excerpta Medica), and BIDS (Institute for Scientific Information). In addition, the bibliographies of eligible articles and reviews were used along with scientific session abstracts in key respiratory- and allergy-based journals. Eligible studies for review provided sufficient information on patient demographics, study design, randomization and control procedures, route of drug administration, measurement of end points, and data analysis.

The main results of this review were qualitative, as it was not possible to perform an overall statistical meta-analysis due to the wide variation in selected end points for a given tissue-specific effect. However, where appropriate, a given end point was analyzed to produce a comparable response across different studies. This was only possible for end points of adrenal suppression, where there were sufficient evaluable data, namely, for effects on 8 AM plasma cortisol or serum cortisol levels and on urinary cortisol (or cortisol-creatinine) excretion (24-hour or overnight). There were 21 eligible studies for urinary cortisol levels and 13 eligible studies for 8 AM cortisol levels, constituting a total of 27 different studies for both end points. For these data, model fitting was applied using multiple regression analysis of slopes to ascertain whether there were significant differences in slope gradients between drugs. The different studies were weighted according to their sample size when performing the regression analysis. Differences between slope gradients were also calculated using 95% confidence intervals (CIs).

The format for this article is first to provide a general overview of factors that determine the systemic bioactivity profile of inhaled corticosteroids, followed by a detailed appraisal of tissue-specific adverse effects, including the results of the meta-analysis for adrenal suppression. It is not within the scope of this article to discuss the antiasthmatic efficacy of inhaled corticosteroids in any detail, as this has been reviewed elsewhere with respect to dose-response relationships and risk-benefit ratio.

PHARMACOLOGIC AND PHARMACOKINETIC DETERMINANTS

Lipophilic substitutions of the basic glucocorticoid nucleus result in compounds that exhibit a high level of receptor potency and affinity, a high degree of local tissue uptake and retention with topical application, and a high degree of first-pass biotransformation in the liver. Corticosteroids administered by inhalation exhibit a high degree of topical potency at the glucocorticoid receptor, and so delivery of low doses may achieve a high local concentration within the airway. The degree of topical potency is assessed conventionally using the skin vasoconstrictor assay. Using this method, an approximate rank-order potency ratio can be calculated for the different inhaled corticosteroids in the following order (from greatest to least potency): fluticasone propionate, budesonide, beclomethasone dipropionate, triamcinolone acetonide, and flunisolide acetate. However, it is probably not possible to extrapolate comparative topical potency data in skin directly to topical antiasthmatic effects in airways or to effects on glucocorticoid receptors in systemic tissues.

The degree of topical activity is also related to the affinity for glucocorticoid receptor binding. Indeed, the rank order for relative receptor affinity is similar to that for potency from the vasoconstrictor assay. The residency time for the receptor-drug complex is also related to the binding affinity, and in this respect the residency half-time is longest for fluticasone. Although a higher level of binding affinity and a longer receptor residency time may result in greater topical efficacy, the same is also likely to be the case in terms of a greater degree of activity at systemic glucocorticoid receptors. In other words, enhanced potency and affinity may cause a commensurate increase in systemic and airway bioactivity profiles. The ratio of airway to systemic activity will also depend on the relative dose-response relationships for airway efficacy and systemic adverse effects. Thus, increasing the dose of inhaled corticosteroid on the flat part of the efficacy curve will confer little further benefit, but at the same time may coincide with the steep part of the systemic curve, resulting in a worse therapeutic index.

Evidence also suggests that the degree of lipophilicity will determine the dwell time at the local tissue site after topical administration. A high degree of lipophilicity will also result in a larger volume of distribution due to more extensive binding within systemic tissues. In this respect, fluticasone has the highest level of lipophilicity among the inhaled corticosteroids, which may in part explain the greater systemic activity of this compound as a consequence of more prolonged systemic tissue retention. Thus, enhanced lipophilicity may represent a 2-edged sword in terms of greater airway and systemic retention.

The specific purpose of inhaled corticosteroid therapy is to target drug delivery directly to the site of airway inflammation. With pressurized metered-dose inhaler devices, most of the dose delivered to the patient is deposited in the oropharynx (>60%), with a much smaller proportion reaching the lungs (<20%). Although there is a small degree of direct absorption from the buccal cavity, most of the oropharyngeal dose is swallowed and subsequently absorbed from the gastrointestinal tract. For all of the inhaled corticosteroids except beclomethasone, there

RESULTS

ADRENAL SUPPRESSION

The administration of exogenous inhaled corticosteroids results in a negative feedback effect on glucocorticoid receptors in the anterior pituitary gland and hypothalamus, which in turn suppresses levels of corticotropin-releasing hormone and corticotropin, respec-
is no first-pass transformation in the lung. Thus, most of the respirable dose delivered to the lung will be bioavailable in the systemic circulation as unchanged active drug. For the swallowed moiety, absorption occurs from the gastrointestinal tract via the portal circulation to the liver, where there is a varying degree of first-pass metabolism to inactive metabolites, ie, 70% for beclomethasone, 90% for budesonide and triamcinolone, and 99% for fluticasone.16-17 The situation for beclomethasone is somewhat different in that there is partial transformation to metabolites that are active (17- beclomethasone monopropionate) and inactive (21- beclomethasone monopropionate).16 It is evident that the lung component of absorption is the larger determinant of the overall systemic bioavailability for inhaled corticosteroids that exhibit a high degree of first-pass inactivation, such as fluticasone, budesonide, and triamcinolone.

It is also pertinent to consider the pharmacokinetic profile and in particular the elimination half-life, as this will determine the degree of accumulation after steady state dosing. Fluticasone propionate has an elimination half-life of 14.4 hours, which is considerably longer than that of other corticosteroids, including budesonide (2.3 hours), triamcinolone (3.6 hours), flunisolide (1.6 hours) and beclomethasone monopropionate (6.5 hours).12,14,17,20-21 Thus, with a 12-hour dosing interval for fluticasone, the average plasma concentration is approximately 1.7 times higher after repeated dosing compared with single dosing.22 This degree of steady state accumulation with fluticasone is in keeping with a 2-fold increase in adrenal suppression between single- and repeated-dose administration.22,23 In contrast, the much shorter elimination half-life of budesonide results in no significant steady state accumulation, and therefore no significant increase in adrenal suppression between single and repeated dosing.23 This emphasizes the need to perform comparative studies at the steady state, as effects with single dosing will be less for a drug with a long elimination half-life.

CLINICAL STUDY DESIGN

When comparing different drugs, it is important to consider their respective delivery devices, as the respirable fraction will determine clinical efficacy and lung absorption. The effects of mouth rinsing or using a spacer will be determined by the degree of first-pass inactivation for the swallowed fraction as well as the increase in respirable dose with a spacer.24-27 In comparing different drugs, it is also important to evaluate a full dose-response curve for a range of usually recommended therapeutic doses. The relative systemic potency ratio can be calculated by comparing 2 drugs on the steep part of their respective dose-response curves using a sufficiently sensitive end point.28-31 It is not valid to make a relative assessment of 2 drugs using arbitrary doses given on the basis of a putative topical potency ratio, eg, comparing beclomethasone with half the dose of fluticasone.32-35 From this type of study, it is not possible to assess whether the observed effect of each drug corresponds to the steep part of its respective dose-response curve. Ideally, the relative potency ratio would be calculated for efficacy and systemic activity in the same study, to assess a comparative therapeutic index for both drugs. In practice, this is extremely difficult to achieve, because the steep part of the dose-response curve for clinical efficacy does not usually coincide with the steep part of the curve for systemic activity.3 Thus, it may not be possible to calculate a true systemic potency ratio for therapeutically equivalent doses of 2 different drugs.

The type of subject used for evaluation may also be an important factor. A reduction in peripheral airway caliper in asthmatic patients may significantly reduce the degree of lung absorption and hence influence the systemic bioactivity.3 Thus, for a given drug, the absolute magnitude of systemic effect may be overestimated if this is evaluated in healthy volunteers who have normal airway caliper.36 Likewise, it may not be possible to extrapolate effects in patients with mild asthma to what happens in patients with more severe asthma due to differences in lung absorption for a given dose. However, when comparing 2 drugs, the relative difference in systemic activity will probably be the same in healthy subjects as in asthmatics, providing that the identical end point is used. Another important factor when studying patients is that there may be effects of previous corticosteroid exposure, eg, as in considering the legacy of previous prednisone treatment.37

The sensitivity of the measured end points for the study will also have a major bearing on the results. For example, in studies looking at adrenal suppression, the timing of spot measurements of early morning cortisol concentration is critical, in that peak levels usually occur no later than 8 AM as a consequence of the normal circadian rhythm.38 Thus, measuring early morning cortisol concentration any later than 8 AM will reduce the sensitivity for detection, and measuring in a 2-hour window between 8 and 10 AM is even less sensitive. This explains the results of studies where there has been only a small detectable effect on early morning cortisol concentration measured at a variable time between 8 and 10 AM in patients receiving fluticasone.33,35,36 Although a given end point of tissue response may be highly sensitive at detecting systemic bioactivity, these effects should be put into proper perspective in terms of clinically relevant adverse effects. The use of knemometry (an electronic method for measuring lower-leg growth) to measure small differences in lower-leg length is a good example of a test that is highly sensitive as a short-term marker of systemic bioactivity in children but does not predict effects of inhaled corticosteroids on long-term growth.

**Table 1.**

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In general terms, there are 2 types of tests of adrenocortical function, namely, screening tests of basal adrenocortical activity and dynamic stimulation tests to assess adrenocortical reserve. The most sensitive way to evaluate basal adrenocortical activity is to perform a 24-hour integrated measurement of plasma cortisol levels. Proper compliance with 24-hour urine collection is also difficult to achieve in an outpatient setting, and hence fractionated collection for overnight moieties is used. Proper compliance with 24-hour urine collection is also difficult to achieve in an outpatient setting, and hence fractionated collection for overnight moieties is used.

Table 1. Dose Response for Adrenal Suppression in Asthmatics

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design (No.)</th>
<th>Treatment (Dose, mg/Delivery Device)</th>
<th>End Points, Time of Sampling/Component Measured</th>
<th>Outcomes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipworth and Wilson, 1998</td>
<td>r, pc, co, sb (12)</td>
<td>Triamcinolone acetonide (0.4-1.6/spacer); budesonide (0.4-1.6/DPI)</td>
<td>8 AM/UCCon</td>
<td>Triamcinolone, NS; budesonide, NS</td>
</tr>
<tr>
<td>Lawrence et al, 1997</td>
<td>r, pc, pg, db (274)</td>
<td>Fluticasone propionate (0.2-1.0/DPI)</td>
<td>8-10 AM</td>
<td>Fluticasone (DPI), 13%</td>
</tr>
<tr>
<td>Clark and Lipworth, 1997</td>
<td>r, pc, co, db (12)</td>
<td>Budesonide (0.5-2.0/spacer); fluticasone propionate (0.5-2.0/DPI)</td>
<td>8 AM/UCCon</td>
<td>Budesonide, NS; fluticasone, 48%; budesonide, NS; fluticasone, 60%</td>
</tr>
<tr>
<td>Wilson et al, 1997</td>
<td>r, pc, co, sb (12)</td>
<td>Triamcinolone acetonide (0.4-1.6/spacer); fluticasone propionate (0.33-1.54/DPI)</td>
<td>8 AM/UCCon</td>
<td>Triamcinolone, NS; fluticasone, 57%; triamcinolone, 34%; fluticasone, 62%</td>
</tr>
<tr>
<td>Agertoft and Pedersen, 1997†</td>
<td>r, pg, op (217)</td>
<td>Fluticasone propionate (0.1-0.4/DPI); budesonide (0.1-0.4/DPI) for 5 wk, taper at each dose (run-in on budesonide [0.4-0.8/spacer])</td>
<td>24 h/UFC</td>
<td>Fluticasone vs budesonide, NS</td>
</tr>
<tr>
<td>Clark et al, 1996</td>
<td>r, pc, co, db (12)</td>
<td>Budesonide (0.4-2.0/pMDI); fluticasone propionate (0.5-2.0/DPI)</td>
<td>8 AM</td>
<td>Budesonide, 26%; fluticasone, 65%</td>
</tr>
<tr>
<td>Kellerman et al, 1996</td>
<td>r, pc, pg, db (118)</td>
<td>Fluticasone propionate (0.5-2.0/DPI); prednisone (10/oral)</td>
<td>Cos 250 μg</td>
<td>Fluticasone, 29%; prednisolone, 37%</td>
</tr>
<tr>
<td>Goldberg et al, 1996</td>
<td>cs, c (39); controls (21)</td>
<td>Beclomethasone dipropionate (0.2-1.0/pMDI and/or spacer) for at least 4 mo</td>
<td>24 h/UCC</td>
<td>Fluticasone, 32%; spacer no effect</td>
</tr>
<tr>
<td>Clark et al, 1996</td>
<td>r, pc, co, sb (10)</td>
<td>Budesonide (0.4-1.25/spacer); fluticasone propionate (0.4-1.25/spacer) as single doses</td>
<td>UCC</td>
<td>Fluticasone, 71%; budesonide, NS</td>
</tr>
<tr>
<td>McCubbin et al, 1995</td>
<td>r, pg op (26)</td>
<td>Beclomethasone dipropionate (0.4-1.6/pMDI); triamcinolone acetonide (0.8-3.2/spacer); flunisolide (1.0-4.pMDI)</td>
<td>24 h/UFC</td>
<td>Beclomethasone, 15%; triamcinolone, 46%; flunisolide, 49%</td>
</tr>
<tr>
<td>Chervinsky et al, 1994</td>
<td>r, pc, pg, db (331)</td>
<td>Fluticasone propionate (0.05-1.0/pMDI)</td>
<td>8 AM</td>
<td>Fluticasone, NS</td>
</tr>
<tr>
<td>Ninan et al, 1993†</td>
<td>cs, c (77); controls (23)</td>
<td>Budesonide (0.8-2.4/spacer or DPI); beclomethasone dipropionate (0.8-2.0/spacer or DPI)</td>
<td>Cos 250 μg</td>
<td>Fluticasone, NS; budesonide, NS</td>
</tr>
<tr>
<td>Dah et al, 1993</td>
<td>r, pg, db (672)</td>
<td>Fluticasone propionate (0.1-0.8/pMDI); beclomethasone dipropionate (0.4/pMDI)</td>
<td>8-10 AM</td>
<td>Fluticasone, 9%; beclomethasone, 6%</td>
</tr>
<tr>
<td>Altman et al, 1992</td>
<td>pg, op (143)</td>
<td>Triamcinolone acetonide (0.8, 1.2, 1.6/spacer)</td>
<td>8 AM</td>
<td>Fluticasone, NS; beclomethasone, NS</td>
</tr>
<tr>
<td>Priftis et al, 1990†</td>
<td>cs, c (25); controls (23)</td>
<td>Beclomethasone dipropionate (0.2-0.9/pMDI) 1-8 y</td>
<td>24 h/UCC</td>
<td>Suppression at &gt;0.4 mg/m² per day</td>
</tr>
<tr>
<td>Bisgaard et al, 1988†</td>
<td>r, pg, db (30)</td>
<td>Beclomethasone dipropionate (0.2-0.8/pMDI); budesonide (0.2-0.8/pMDI) 12 wk</td>
<td>Cos 125 μg</td>
<td>Beclomethasone, 36%; budesonide, NS</td>
</tr>
<tr>
<td>Pedersen and Fuglsang, 1988†</td>
<td>r, co, op (31)</td>
<td>Budesonide (0.8-1.2/pMDI and/or spacer); beclomethasone dipropionate (0.8-1.2/pMDI and/or spacer) 6 wk</td>
<td>24 h/UFC</td>
<td>Beclomethasone, 25% lower than budesonide</td>
</tr>
</tbody>
</table>

* Studies were included that evaluated at least 3 doses of inhaled corticosteroid in asthmatic children and adults. r indicates randomized; c, controlled; pc, placebo controlled; pg, parallel group; co, crossover; op, open; sb, single blind; db, double blind; cs, cross-sectional; pMDI, pressurized metered-dose inhaler; DPI, dry-powder inhaler; UFC, urinary free cortisol; UCC, urinary cortisol-creatinine ratio; UCM, urinary cortisol metabolites; on, fractionated collection for overnight moiety; Cos, dose of cosyntropin stimulation (µg, 250 µg); and NS, no significant suppression at maximal evaluated dose.
† Indicates study in children; all other studies were performed in asthmatic adults.
‡ Response is shown as maximal percentage suppression (where a significant response occurred).
T HE PURPOSE of a dynamic stimulation test with corticotropin or corticotropin-releasing hormone is to assess whether there is any impairment of adrenal cortical reserve that might occur in response to physiological stressful stimuli. When using a synthetic corticotropin (ie, cosyntrropin) stimulation test, it is important to use the correct dose that mimics a physiological stress response. In this respect, the conventional 250-g dose of cosyntrropin is 500 times the dose required for a stimulated cortisol response, and as such represents a supraphysiological dose of corticotropin. The 0.5-g dose of cosyntrropin is as effective at producing a stimulated cortisol response and has been shown to correlate well with results of an insulin stress test and is therefore superior to the 250-g dose in detecting impaired adrenal reserve.

Comparative dose-response studies in healthy volunteers for fluticasone and budesonide given by metered-dose inhaler have shown relative potency ratios (fluticasone-budesonide) of 2.9 and 3.7 for suppression of integrated 24-hour plasma cortisol levels and of 3.1 and 5.2 for suppression of 8 AM plasma cortisol levels. This compares with a relative potency ratio of 3.5 for suppression of 8 AM cortisol levels obtained from a dose-response study in asthmatic patients given fluticasone and budesonide via metered-dose inhaler. In a different study in healthy volunteers, a dose comparison was performed with budesonide and fluticasone given via their respective dry-powder inhaler devices, which showed a relative potency ratio of 1.7 for 24-hour cortisol levels and 2.3 for 8 AM cortisol levels. The lower potency ratios for fluticasone vs budesonide when given via dry-powder inhalers reflect the greater drug delivery to the lung from the budesonide Turbuhaler (a reservoir dry-powder inhaler) compared with the fluticasone Diskhaler device (a blister dry-powder device), whereas the fluticasone metered-dose inhaler delivers more drug than the budesonide metered-dose inhaler. The reason for the higher ratio with 8 AM than with 24-hour cortisol levels probably reflects the longer elimination half-life of fluticasone, such that there will be higher levels of fluticasone at 8 AM when used with a 12-hour dosing interval.

When comparing both drugs given via the metered-dose inhaler device, assuming half the dose of fluticasone is therapeutically equivalent to 1 dose of budesonide, this would result in fluticasone exhibiting approximately 1.7-fold greater systemic activity, on the assumption of a relative potency ratio of 3.5:1 for cortisol suppression. The budesonide Turbuhaler and fluticasone Diskhaler are therapeutically equivalent on a milligram-for-milligram basis, whereas the fluticasone Diskhaler exhibits 1.7-fold greater adrenal suppression than the budesonide Turbuhaler. This shows that differences in glucocorticoid receptor potency alone cannot account for the 1.7-fold greater adrenal suppression seen with fluticasone. The greater degree of systemic bioactivity with fluticasone probably represents a complex interplay of factors, including accumulation in blood, retention in systemic tissue, and prolonged receptor occupancy.

These studies do not provide information on the relative therapeutic index of each drug, as there is no commensurate evaluation of antiasthmatic clinical efficacy. In the study by Ayres et al of patients with severe asthma, doubling the 1-mg/d dose of fluticasone propionate resulted in no improvement in antiasthmatic efficacy, but was associated with a highly significant increase in adrenal suppression. This suggests that even for high-potency drugs such as fluticasone propionate, there is likely to be a greater falloff in the risk-benefit ratio for doses above 1 mg/d. In the same study, 2-mg/d fluticasone propionate was no more effective than 1.6 mg of budesonide, but was associated with a significantly greater level of cortisol suppression, indicating that in patients with severe asthma, the use of a higher-potency drug may not necessarily be associated with an improvement in the therapeutic index.

The effects of inhaled corticosteroids have also been compared with those of oral corticosteroids in dose-response studies. In a dose-ranging study in asthmatic patients, fluticasone propionate (0.44-1.76 mg/d) given via large-volume spacer produced dose-related suppression of 8 AM cortisol levels, which was comparable to that of prednisolone (5-20 mg/d), with maximal suppression amounting to 56% with fluticasone propionate (1.76 mg) vs 67% with oral prednisolone (20 mg). The calculated relative milligram potency ratio for fluticasone vs prednisolone was 8.5:1 (95% CI, 5.7-11.2). Too good et al compared oral prednisone and inhaled budesonide (via large-volume spacer) in terms of their relative efficacy and cortisol suppression. In patients who were not dependent on prednisone, the relative potency ratio (budesonide vs prednisone) for efficacy was 56:1, with the relative ratio for cortisol suppression being 9:1, resulting in a relative therapeutic index of 6:1. In patients who were dependent on prednisone, the ratios for efficacy and cortisol suppression were 60:1 and 8:1, respectively, resulting in a relative therapeutic index of 7:1.

With all inhaled corticosteroids given at high dosage, there is likely to be a dual effect due to topical bioactivity from the airway dose as well as prednisonelike activity from the systemic bioavailable dose. The component of systemic bioactivity is therefore likely to be greater with fluticasone, which along with its topical potency may contribute to its antiasthmatic effects when given at high doses. This may partially explain why it is possible to wean patients from oral prednisone maintenance therapy by using high-dose inhaled fluticasone. In other words, systemic prednisone is being substituted with systemic fluticasone. This is supported by the observation of a persistent degree of cortisol suppression in patients who are weaned from prednisone therapy by treatment with high-dose fluticasone propionate (2 mg/d). After 16 weeks of treatment with fluticasone, despite weaning to a mean prednisone dose of only 0.9 mg/d, there were persistently abnormal early morning cortisol values in 73% of patients, although this was associated with
A 22% improvement in morning peak flow. This suggests that patients who are weaned from oral prednisone therapy with high-dose inhaled corticosteroids should be closely monitored for evidence of persistent impaired adrenal function, and particularly when using high-potency drugs such as fluticasone.

Most studies in asthmatic children have shown that with doses of inhaled corticosteroid of 0.4 mg/d or less, irrespective of drug or delivery device, there is no evidence of detectable adrenal suppression. There are, however, 2 noteworthy exceptions. First, Agertoft and Pedersen showed that dry-powder formulations of fluticasone propionate and budesonide, in doses of 0.2 mg/d and 0.4 mg/d, respectively, for 2 weeks, produced significant suppression of 24-hour urinary cortisol-creatinine excretion, with fluticasone causing greater suppression. Second, Nicolaizik et al showed that budesonide and beclomethasone dipropionate (given via metered-dose inhaler) at 0.4 mg/d for 2 weeks produced comparable suppression of integrated overnight serum cortisol profile and 24-hour urinary free cortisol levels, although this study was open and not placebo controlled. Studies of doses greater than 0.4 mg/d given via spacer have shown fluticasone propionate and beclomethasone dipropionate to produce greater suppression of urinary cortisol-creatinine excretion than budesonide. These findings once again emphasize the importance of always trying to taper doses to attain the lowest possible maintenance dose for adequate long-term asthma control in children.

It is probably more clinically relevant to look at individual data for abnormally low cortisol values rather than to evaluate the statistical significance of mean responses. For the reasons discussed previously, it is pertinent to evaluate absolute cortisol values in studies of asthmatic patients but not in healthy volunteers. In a study by Clark et al of asthmatic children, 18 of 30 patients had low cortisol values when given fluticasone propionate compared with 6 of 30 when given budesonide, in terms of overnight urinary cortisol excretion, when both drugs were given via a large-volume spacer with a dose range of 0.4 to 1.25 mg/d. In adult asthmatics, 21 of 36 had low overnight urinary cortisol measurements when given fluticasone propionate vs 3 of 36 when given budesonide, when both drugs were given with a dose range of 0.5 to 2.0 mg/d via metered-dose inhaler alone. In the same study, for doses of up to 1 mg/d, 14 of 24 vs 1 of 24 had low cortisol values when given fluticasone propionate and budesonide, respectively.

The likelihood of impaired adrenal reserve and insufficient cortisol response to stress can be evaluated using a dynamic stimulation test. Smith and Hodson studied 54 asthmatic adults receiving long-term beclomethasone dipropionate therapy via metered-dose inhaler in doses ranging from 0.5 to 2.0 mg/d with no concurrent oral corticosteroid therapy. Evidence of adrenal suppression was found in terms of subnormal plasma cortisol levels before and after stimulation with 250 µg of cosyntropin in 4 of 11 patients taking 2.0 mg/d. Brown et al studied a group of 78 adults with asthma who had been receiving long-term inhaled corticosteroid therapy, with evidence of adrenal suppression being identified at results of screening in 16 of the patients who were taking high-dose beclomethasone dipropionate (1.5-2.0 mg/d) and 10 who had received previous long-term systemic steroid therapy. Fourteen of 16 patients had subnormal cortisol values after cosyntropin stimulation (250 µg), with 12 of these patients also having subnormal 24-hour urinary cortisol excretion. In a multicenter parallel group study of 143 adults with asthma given 6-month treatment with 0.8, 1.2, or 1.6 mg/d of triamcinolone acetonide via spacer, all doses produced significant suppression of mean 24-hour urinary free cortisol levels but had no significant effect on mean 8 AM plasma cortisol levels or the response to cosyntropin stimulation (250 µg). These data are consistent with the findings of Wilson et al where triamcinolone acetonide, 1.6 mg/d, or flunisolide acetate, 2 mg/d, produced significant suppression of overnight and early morning urinary cortisol-creatinine excretion, but exhibited no significant effect on 8 AM cortisol levels or on response to cosyntropin stimulation (0.5 µg).

META-ANALYSIS OF ADRENAL SUPPRESSION STUDIES

A meta-analysis of 21 studies of urinary cortisol levels (Figure 1) and 13 studies of suppression of 8 AM plasma cortisol levels (Figure 2) revealed fluticasone to exhibit significantly steeper dose-related systemic bioactivity than beclomethasone, budesonide, or triamcinolone. The variables from the regression analysis are shown in Table 2 and Table 3 for urinary and for plasma cortisol suppression, respectively. There were significant differences between the slope gradients for urinary cortisol levels when comparing fluticasone with beclomethasone, triamcinolone, or budesonide; whereas for 8 AM plasma cortisol level, the slope for fluticasone was significantly different than that for budesonide or triamcinolone. There were no significant differences among beclomethasone, budesonide, or triamcinolone for their effects on urinary or plasma cortisol levels.

These effects were most apparent at doses above 0.8 mg/d, due to the differences in slope gradients between fluticasone and the other drugs. It was also evident from the data on 8 AM plasma cortisol suppression that there were no significant differences in slopes between fluticasone and prednisolone when both drugs were compared on a putative 1:10-mg equivalent basis. As differences between fluticasone and the other inhaled corticosteroids were not parallel across the dose range, this indicated that a difference in glucocorticoid receptor potency was probably not the main reason for the greater systemic bioactivity exhibited by fluticasone. When comparing the same degree of urinary cortisol suppression, it was evident that 1.6 mg of triamcinolone acetone and 0.4 mg of fluticasone propionate were approximately equivalent.

GROWTH

Any chronic disease process, including asthma, may affect growth. Chronic asthma that is not adequately controlled may result in attenuation of the prepubertal growth spurt, a delay in puberty and the associated pubertal
growth spurt, followed by a catch-up phase toward final attained adult height. The effect of the asthmatic disease process itself thus may have an important confounding effect in interpreting effects on growth due to exogenous corticosteroid therapy. Normal growth occurs rapidly during the first 3 years of life and is predominantly determined by nutritional status. This is then followed by childhood growth up until puberty, dependent on growth hormone secretion from the anterior pituitary gland, followed by the pubertal growth spurt, which is also driven by the sex steroid hormones.

The most important outcome measure is long-term growth as assessed by final adult height and compared with the predicted values for sex and midparental height. In practice, this type of longitudinal type cohort follow-up studies is difficult to perform. Thus, most studies have evaluated effects on medium-term growth for a period of months or years using a calibrated stadiometer to measure height (Table 4). The main outcome measures of such studies are usually expressed as the height velocity (or growth rate) or stature height compared with sex- and age-matched normal standards, expressed as height standard deviation score or height centiles. Such measurements are affected by growth rate during childhood, seasonal effects of growth, and timing of the pubertal growth spurt. For this reason, results of medium-term growth studies may not predict effects on final attained adult height.

It is also important to consider the effects of corticosteroids on bone age as well as growth rate. Providing that growth rate and bone age are reduced to a comparable degree, the child may retain the full potential for catch-up growth to achieve normal predicted adult height. If growth rate is attenuated more than bone age, it is possible that final height may be adversely affected.

Long-term maintenance therapy with oral corticosteroids is known to suppress growth in children. Current guidelines for the treatment of childhood asthma now suggest the use of early intervention with inhaled corticosteroids as the mainstay of preventive therapy, as this has been shown to prevent disease progression in terms of reversible airway damage as a consequence of untreated inflammation. For most children with asthma, effective long-term control can be achieved with low doses of inhaled corticosteroids (<0.4 mg/d), which are associated with minimal, if any, detectable systemic bioactivity.

Studies measuring short-term lower-leg growth using knemometry have shown that dose-related suppression with inhaled corticosteroids occurs to a lesser degree than with oral prednisolone. In general, studies of inhaled corticosteroids have shown detectable effects on knemometry at doses of 0.4 mg/d or above. It has been shown subsequently that short-term effects on knemometry do not predict effects on long-term growth using a properly calibrated stadiometer to measure stature height. Thus, knemometry should be regarded merely as a highly sensitive marker of potential systemic bioactivity but not a clinically relevant measure of growth effects with inhaled corticosteroids.

Two 12-month studies comparing monotherapy with dry-powder beclomethasone dipropionate, 0.4 mg/d, and salmeterol xinafoate, 50 g twice daily, showed beclomethasone to be superior in terms of disease control and airway hyperreactivity, although it was associated with a small but significant reduction in height velocity of 1.08 to 1.40 cm/y. In another 12-month study comparing monotherapy with beclomethasone dipropionate via pressurized metered-dose inhaler, 0.336 mg/d, or optimized twice-daily theophylline, beclomethasone resulted in comparable symptom control with less bronchodilator use, fewer res-

References 23, 31, 42, 44, 46, 49, 50, 54, 56, 58, 68, 70, 72, 73, 75, 88-93.

and triamcinolone (Figure 2). Ellipses indicate not applicable.

However, in a meta-analysis of 12 other medium-term studies with beclomethasone dipropionate (dose range, 0.2-0.9 mg/d), there was no association between its use and adverse growth effects, in contrast to significant growth impairment observed in 8 studies with prednisone.112

There are only 2 long-term studies that have looked at final adult height in children receiving inhaled corticosteroids. Balfour-Lynn113 showed that although puberty was delayed, treatment with beclomethasone dipropionate, 0.4 to 0.6 mg/d, did not adversely affect subsequent catch-up growth, which resulted in the attainment of normal predicted adult height. In a more recent prospective cohort study, 153 patients with asthma, of whom 58 were receiving corticosteroid therapy, were compared with 153 age- and sex-matched nonasthmatic controls.103 The adult height of asthmatic children adjusted for midparental height was not significantly different from that of controls, and there was also no significant overall effect of inhaled or oral corticosteroid exposure. These results of long-term follow-up studies are therefore reassuring and suggest that suppressing asthmatic disease activity in children will usually outweigh any potential systemic bioactivity of inhaled corticosteroids in determining long-term growth. However, it is worth mentioning that all of the data (published and unpublished) on growth were recently reviewed at a meeting of the Food and Drug Administration Pulmonary-Endocrine Drugs Advisory Committee (Bethesda, Md, July 30-31, 1998), where a consensus decision was made to alter class labeling for all intranasal and inhaled corticosteroids in children to include a precautionary statement that the use of recommended doses may be associated with a reduction in growth velocity.

**BONE METABOLISM**

One of the greatest concerns of long-term corticosteroid therapy for asthma is its potential for adverse effects on bone turnover, resulting in an increased risk for osteoporosis and fracture. Bone tissue undergoes a constant metabolic turnover and remodeling process throughout adult life. This reflects a fine balance in the bone matrix in terms of the activity of bone-forming (osteoblasts) and bone-breakdown cells (osteoclasts). Uncoupling of this equilibrium of osteoblasts and osteoclasts may

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### Table 2. Regression Variables for Urinary Cortisol Suppression*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Slope Gradient (P)</th>
<th>95% Confidence Interval vs Fluticasone Propionate</th>
<th>Difference vs Fluticasone Propionate (P)</th>
<th>95% Confidence Interval vs Prednisolone</th>
<th>Difference vs Prednisolone (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone propionate</td>
<td>63.2 (.&lt;.001)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Budesonide</td>
<td>32.5 (.01)</td>
<td>1.0 to 60.6</td>
<td>1.9-fold (&lt;.05)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>17.3 (.36)</td>
<td>3.7 to 88.1</td>
<td>3.7-fold (&lt;.05)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Budesonide</td>
<td>14.7 (.14)</td>
<td>20.9 to 76.1</td>
<td>4.3-fold (&lt;.001)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

* Values for slope gradients and 95% confidence intervals are shown as logarithm units taken from the regression of logarithm dose response. There were no significant differences among beclomethasone, triamcinolone, and budesonide (Figure 1). Ellipses indicate not applicable.

### Table 3. Regression Variables for 8 AM Plasma Cortisol Suppression*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Slope Gradient (P)</th>
<th>95% Confidence Interval vs Fluticasone</th>
<th>Difference vs Fluticasone (P)</th>
<th>95% Confidence Interval vs Prednisolone</th>
<th>Difference vs Prednisolone (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluticasone propionate</td>
<td>86.6 (.&lt;.001)</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>79.7 (.&lt;.001)</td>
<td>−38.0 to 51.6</td>
<td>1.1-fold (.76)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Budesonide</td>
<td>23.6 (.&lt;.05)</td>
<td>36.7 to 89.1</td>
<td>3.7-fold (&lt;.001)</td>
<td>10.8-101.6</td>
<td>3.4-fold (&lt;.05)</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>19.1 (.34)</td>
<td>24.2 to 110.6</td>
<td>4.5-fold (&lt;.005)</td>
<td>3.6-117.6</td>
<td>4.2-fold (&lt;.05)</td>
</tr>
</tbody>
</table>

* Values for slope gradients and 95% confidence intervals are shown as logarithm units taken from the regression of logarithm dose response. Oral and inhaled corticosteroids were compared on a putative dose equivalence of 10.1 mg for the regression analysis. There were no significant differences between budesonide and triamcinolone (Figure 2). Ellipses indicate not applicable.
cause a reduction in bone mass, resulting in osteoporosis and ultimately increased fracture risk. Corticosteroids tend to affect bone predominantly in the axial skeleton (ie, the vertebrae), which contains a higher proportion of the more metabolically active trabecular bone than cortical bone. The mechanism for corticosteroid-induced bone loss is complex and involves suppression of osteoblast function, increased bone resorption due to attenuated sex hormone secretion, and increased parathyroid hormone levels due to attenuated bowel and renal calcium absorption.

The bone mass at any given time of life represents a complex interplay of genetic loading and other risk factors such as age, ethnic origin, sex, body size, diet, use of alcohol and tobacco, physical activity, thyroid status, and sex hormone status. The radiological measurement of bone mass may be used to assess the risk for development of osteoporosis, when measured at appropriate sites such as the lumbar vertebrae or proximal femur. There are, however, a number of sensitive biochemical markers of bone metabolism, although these can be considered only as a surrogate for the criterion standard measurement of bone density. Biochemical markers of bone formation include levels of alkaline phosphatase, osteocalcin, procollagen type 1 carboxyterminal and amino-terminal propeptide, and procollagen type 3 amino-terminal propeptide, all of which are measured in serum. Bone resorption markers include levels of urinary hy-

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design (No.)</th>
<th>Treatment (Dose, mg/Delivery Device)</th>
<th>End Points</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al, 1998</td>
<td>r, pc, pg, db (325); mean age, 8.1 y (range, 4-11 y)</td>
<td>Fluticasone propionate (0.1, 0.2/DPI) or placebo, for 12 mo</td>
<td>Height velocity</td>
<td>No significant effect of fluticasone</td>
</tr>
<tr>
<td>McCowan et al, 1998</td>
<td>Prospective cohort; asthmatic patients (235); mean age, 10 y (range, 1-15 y), compared with reference population</td>
<td>Treatment stratified according to British Thoracic Society guidelines</td>
<td>Height SDS</td>
<td>Reduction $= -0.62$ with inhaled steroids $0.4$ mg/dl, independent of effect of social deprivation</td>
</tr>
<tr>
<td>Simons, 1997</td>
<td>r, pc, pg, db (241); mean age, 9.3 y (range, 6-14 y)</td>
<td>Beclomethasone dipropionate (0.4/DPI), salmeterol xinafoate, placebo for 12 mo</td>
<td>Height velocity</td>
<td>1.06-cm/y reduction with beclomethasone vs placebo ($P &lt; .05$)</td>
</tr>
<tr>
<td>Verbeke et al, 1997</td>
<td>r, pg, db (241); mean age, 10.5 y (range, 6-16 y)</td>
<td>Beclomethasone dipropionate (0.4/DPI) or salmeterol xinafoate for 12 mo</td>
<td>Height velocity</td>
<td>1.4-cm/y reduction with beclomethasone vs salmeterol ($P &lt; .01$)</td>
</tr>
<tr>
<td>Silverstein et al, 1997</td>
<td>Retrospective cohort; asthma patients (153)</td>
<td>Oral or inhaled steroid as cumulative adjusted exposure vs prednisone</td>
<td>Adult height (adjusted to midparental height)</td>
<td>No significant overall effect of steroid exposure</td>
</tr>
<tr>
<td>Price et al, 1997</td>
<td>r, pg, op (60); age range, 4-10 y</td>
<td>Fluticasone propionate (0.1/DPI) or cromolyn sodium for 12 mo</td>
<td>Height velocity and height SDS</td>
<td>No significant effect of fluticasone</td>
</tr>
<tr>
<td>Doull et al, 1995</td>
<td>r, pc, pg, db (84); mean age, 8.3 y (range, 7-9 y); matched asthmatic controls without steroid (62)</td>
<td>Beclomethasone dipropionate (0.4/DPI) or placebo for 7 mo</td>
<td>Height velocity</td>
<td>1.0-cm reduction with beclomethasone vs placebo ($P &lt; .001$)</td>
</tr>
<tr>
<td>Agertoft and Pedersen, 1994</td>
<td>Prospective cohort, c, pg, op (216); mean age, 6.2 y (range, 3-11 y); matched asthmatic controls without steroid (62)</td>
<td>Budesonide (0.43-0.71/spacer or DPI), dose tapering for 3-7 y after initial 1-2 y run-in without steroid</td>
<td>Height velocity and height SDS</td>
<td>No overall significant effect of budesonide vs run-in or controls</td>
</tr>
<tr>
<td>Tinkelman et al, 1993</td>
<td>r, pc, pg, db (195); mean age, 11.9 y (range, 6-16 y)</td>
<td>Beclomethasone dipropionate (0.336/pMDI) or theophylline for 12 mo</td>
<td>Height velocity</td>
<td>1.6-cm/y reduction with budesonide vs theophylline ($P = .001$)</td>
</tr>
<tr>
<td>Merkus et al, 1993</td>
<td>r, pc, pg, db (40); mean age, 12.8 y (range, 12-16 y); matched nonasthmatic subjects (80); mean age, 12 y</td>
<td>Albuterol sulfate and budesonide (0.6/pMDI) or albuterol sulfate and placebo for 22 mo</td>
<td>Height velocity</td>
<td>No significant effect of budesonide</td>
</tr>
<tr>
<td>Littlewood et al, 1998</td>
<td>Retrospective cohort; taking beclomethasone dipropionate (81); mean age, 10.9 y; unmatched asthmatic controls (249); mean age, 6.6 y</td>
<td>Beclomethasone dipropionate (0.2-0.8/DPI)</td>
<td>Height SDS</td>
<td>Overall reduction with beclomethasone, 0.39 vs controls, 0.14 ($P &lt; .01$); also $P &lt; .05$ for before vs after beclomethasone therapy ($n = 16$)</td>
</tr>
<tr>
<td>Nassif et al, 1987</td>
<td>Prospective cohort; taking beclomethasone dipropionate (32); mean age, 13 y; prednisone taking alternate day (24); mean age, 10 y; asthmatic controls (20); mean age, 13 y; nonasthmatic subjects (21); mean age, 12 y</td>
<td>Beclomethasone dipropionate (mean dose, 0.53); prednisone, 29 alternate days</td>
<td>Height centiles</td>
<td>Trend toward reduction in beclomethasone and prednisone groups related to dose</td>
</tr>
</tbody>
</table>

*SDS indicates height SD score. Other abbreviations are given in the first footnote to Table 1.*
inhaled corticosteroid. However, bone markers such as osteocalcin levels compared with controls not receiving beclomethasone or budesonide therapy have shown lower bone metabolism may be relatively more resistant to the effects of corticosteroids from one tissue to another, and if anything, treatment with corticosteroids, with osteocalcin being the marker of choice because of its sensitivity, specificity, and reproducibility.

Short- and medium-term studies of healthy volunteers and asthmatic patients receiving inhaled corticosteroids have been able to detect dose-related effects on biochemical bone markers, which occur less frequently than with oral corticosteroids. In the study of Jennings et al, from the steep part of the dose-response curves it was possible to calculate relative potency ratios on a milligram equivalent basis for budesonide vs prednisolone, showing a ratio of 2.9:1 for osteocalcin suppression and 5.0:1 for cortisol suppression. These data therefore suggest that it may not be possible to extrapolate directly the systemic effects of corticosteroids from one tissue to another, and if anything, bone metabolism may be relatively more resistant to the adverse effects to corticosteroid therapy. Cross-sectional studies in asthmatic patients receiving long-term beclomethasone or budesonide therapy have shown lower osteocalcin levels compared with controls not receiving inhaled corticosteroid. However, bone markers cannot be used as a surrogate for bone density to predict the risk for development of osteoporosis.

There are surprisingly few long-term controlled studies that have evaluated effects of corticosteroids on bone density in asthmatic children or adults (Table 5). In 157 asthmatic children receiving inhaled budesonide for 3 to 6 years, bone density measurement was not significantly different compared with that in asthmatic controls who had not received steroids. There was also no relationship between bone density and duration of treatment or in terms of current and accumulated dose of budesonide. In a cross-sectional study of asthmatic adults receiving long-term corticosteroid therapy, there was a decrease in bone density that was associated with the daily dose of inhaled corticosteroid and years of prednisone use. In a subgroup analysis of 41 postmenopausal asthmatic women from this study, increased bone density was found to be associated with the number of years of supplemental estrogen therapy, suggesting that this may have a protective effect against corticosteroid-induced osteoporosis in this high-risk group of patients.

More recently, Wisniewski et al found no difference in bone density between asthmatic patients taking corticosteroids and unmatched asthmatic controls who were not taking inhaled corticosteroids. In this study, there was an association between the cumulative inhaled dose of corticosteroid and reduced lumbar bone density, but only in women. Ip et al also showed reduced bone density in asthmatics receiving inhaled corticosteroids compared with nonasthmatic controls, the effect being predominantly observed in women. There was also an association of daily dose of inhaled corticosteroids and reduced lumbar bone density in asthmatic women. Many of the studies looking at bone density are difficult to interpret because of their relatively small sample size or because of confounding due to the legacy of previous oral corticosteroid exposure. However, postmenopausal asthmatic women are at particular risk and should if possible receive concomitant estrogen replacement therapy, which also has other benefits in terms of mood, skin, and vascular sequelae.

**OCULAR EFFECTS**

The use of systemic corticosteroids is an established risk factor in the development of posterior subcapsular cataracts. In a review published in 1986 surveying 9 previous studies among 343 asthmatics treated with corticosteroids, the prevalence of posterior subcapsular cataracts was found to range from 0% to 54%, with an average of 9%. The prevalence was influenced by the daily cumulative dose of corticosteroids as well as by age and ethnic origin. Previous case reports of posterior subcapsular cataracts in patients taking inhaled corticosteroids are often confounded by previous exposure to oral corticosteroid therapy. Indeed, resolution of posterior subcapsular cataracts has occasionally been observed after conversion from maintenance prednisone to inhaled corticosteroid therapy, suggesting a possible dynamic component in early cases.

Toogood et al studied 48 patients (mean age, 61 years) receiving long-term inhaled budesonide or beclomethasone dipropionate with a mean dose of 1.5 mg/d, and found a 27% prevalence of posterior subcapsular cataracts as well as a correlation of the dose and duration of prednisone but not inhaled corticosteroid therapy. Simons et al found no posterior subcapsular cataracts in 95 patients with asthma (mean age, 13.8 years), with a mean dose of budesonide or beclomethasone dipropionate of 0.75 mg/d for a mean duration of 5 years, in whom 77% had no exposure to oral corticosteroids in the past year. Abuekheit et al found no association of posterior subcapsular cataracts with inhaled corticosteroid use in 140 patients with asthma (mean age, 12.2 years) with a treatment duration of more than 5 years, and only 1 patient who was receiving frequent prednisone therapy had cataracts.

More recently, Cumming et al conducted a population-based cross-sectional study that identified 370 patients using inhaled corticosteroids. In these subjects, after adjustment for age and sex, the relative prevalence ratio for corticosteroid vs no corticosteroid exposure was 1.9 (95% CI, 1.3-2.8) for posterior subcapsular, 1.5 (95% CI, 1.2-1.9) for nuclear, and 1.1 (95% CI, 0.9-1.3) for cortical cataracts. The relative prevalence ratio of posterior subcapsular cataracts for a lifetime dose of beclomethasone greater than 2000 mg was 5.5 (95% CI, 2.3-13.0). This study suggests an increased risk for posterior subcapsular cataracts in patients receiving long-term high-dose inhaled corticosteroid therapy, at least with beclomethasone dipropionate. Nonetheless, the relative risk is likely to be lower with high-dose inhaled corticosteroid compared with oral prednisone therapy, in terms of the relative doses required for comparable long-term asthma control.

There have also been case reports suggesting that systemic bioactivity of inhaled or intranasal corticoste-
Glucocorticoids might result in ocular hypertension or open-angle glaucoma.144,145 This was investigated in a recent case-control study of 9793 patients with open-angle glaucoma or ocular hypertension, compared with 38,325 randomly selected controls.146 Odds ratios for ocular hypertension or open-angle glaucoma were determined in patients using inhaled or intranasal glucocorticosteroids relative to nonusers, adjusted for age, sex, diabetes, systemic hypertension, and the use of ophthalmic or oral corticosteroids. Overall results showed that there was no association between current use of inhaled or intranasal corticosteroids and an increased risk for ocular hypertension or open-angle glaucoma. However, those patients who were currently using high doses of corticosteroids on a regular basis for 3 or more months were at a small, significantly increased risk, with a calculated odds ratio of 1.5.

Table 5. Controlled Studies of Bone Density in Asthmatic Children and Adults

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design (No.)</th>
<th>Treatment (Dose, mg/Delivery Device)</th>
<th>End Points/Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agertoft and Pedersen,</td>
<td>Cross-sectional; asthmatic children receiving inhaled steroid for 3-6 y (57); age-matched asthmatic steroid-naive controls (11)</td>
<td>Budesonide (0.2-1.3; mean, 0.5/spacer, DPI) for 4.5 y</td>
<td>DXA: lumbar/no difference in BMD between steroid and nonsteroid groups; bone density not related to treatment duration, accumulated or current dose of budesonide</td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wisniewski et al,139</td>
<td>Cross-sectional; receiving inhaled steroid (47); mean age, 32 y (28 women); unmatched asthmatic controls receiving no steroid (34); mean age, 28 y (15 women)</td>
<td>Budesonide dipropionate (n = 41); budesonide (0.1-3.0; mean, 0.62/pMDI or DPI) for 7.8 y</td>
<td>DXA: lumbar, femur, radius/no difference in BMD between steroid vs nonsteroid groups; cumulative inhaled dose associated with reduced lumbar BMD in women: no association with vertebral fracture</td>
</tr>
<tr>
<td>1997</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luengo et al,127</td>
<td>Longitudinal; receiving inhaled steroid (48); mean age 56 y (33 women); nonasthmatic controls (48)</td>
<td>Budesonide and/or beclomethasone (0.3-1.0, mean 0.66/device not specified) for 2 y</td>
<td>DXA: lumbar/no difference in BMD between asthmatics and nonasthmatics; no correlation with dose or duration of inhaled steroid; no difference between patients with or without coarse of oral steroid</td>
</tr>
<tr>
<td>1997</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinati et al,128</td>
<td>Cross-sectional; receiving inhaled beclomethasone dipropionate (44); mean age, 6.7 y (prepubertal); matched asthmatic controls receiving cromolyn sodium (20)</td>
<td>Beclomethasone dipropionate (0.15-0.6); mean 0.32/device not specified for 6.7 mo</td>
<td>DXA: lumbar; DPA: radius/no effect of beclomethasone on BMD</td>
</tr>
<tr>
<td>1996</td>
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<tr>
<td>Hanania et al,132</td>
<td>Cross-sectional; receiving inhaled steroid (18); mean age, 37 y (12 women); matched asthmatic patients receiving no steroid (18)</td>
<td>Beclomethasone dipropionate and/or beclomethasone (0.8-2.0; mean 1.32/pMDI, spacer and DPI) for 30 mo</td>
<td>DXA: lumbar, femur/inhaled dose and duration associated with reduced BMD in femoral neck; no reduction in BMD in lumbar spine or Wards triangle</td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toogood et al,129</td>
<td>Cross-sectional (69); mean age, 60 y (43 women, 41 postmenopausal) Taking inhaled steroid (69)</td>
<td>Beclomethasone dipropionate and/or budesonide; mean, 1.3/spacer for 10.1 y</td>
<td>DXA/DPA: lumbar/decreased BMD associated with daily dose of inhaled steroids and with years of prednisone therapy; increased BMD associated with years of supplemental estrogen therapy</td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ip et al,130</td>
<td>Cross-sectional; receiving inhaled steroid (30); mean age, 33 y (18 women); matched nonasthmatic controls (30)</td>
<td>Beclomethasone dipropionate (0.2-2.4, mean 1.1/device not specified) for 40 mo</td>
<td>DXA: lumbar, femur/decreased BMD in asthmatic vs nonasthmatic subjects, mainly women; association of daily inhaled dose and reduced lumbar BMD in women</td>
</tr>
<tr>
<td>1994</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baraldi et al,131</td>
<td>Longitudinal; receiving inhaled steroid (14); mean age, 9.1 y; matched asthmatic patients receiving no steroids (16)</td>
<td>Beclomethasone dipropionate (0.3-0.4/spacer) for 6 mo</td>
<td>DXA: lumbar/no effect of beclomethasone on BMD</td>
</tr>
<tr>
<td>1994</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Herrera et al,132</td>
<td>Longitudinal; women receiving inhaled steroids (19); mean age, 53 y (13 postmenopausal); matched nonasthmatic women (19, 13 postmenopausal)</td>
<td>Beclomethasone dipropionate (1.0/spacer) for 12 mo</td>
<td>DXA: lumbar, femur/no effects of beclomethasone on BMD</td>
</tr>
<tr>
<td>1994</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packe et al,135</td>
<td>Cross-sectional Receiving inhaled and intermittent systemic steroids (20); mean age, 38 y Receiving inhaled and continuous systemic steroid (20); mean age, 39 y Receiving no steroid (17); mean age, 36 y</td>
<td>Beclomethasone dipropionate (1.1-2.0/device not specified) for 3 y Prednisolone (7 mg) for 8 y</td>
<td>CT: lumbar/reduced BMD in both beclomethasone and prednisolone groups vs bronchodilator group</td>
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*DXA indicates dual energy X-ray absorptiometry; DPA, dual energy photon absorptiometry; CT, computed tomography; and BMD, bone mineral density. Other abbreviations are given in the first footnote to Table 1.
SKIN EFFECTS

Thinning and bruising of the skin may occur while taking inhaled corticosteroids, with evidence of a dose-response effect. Capewell et al. performed ultrasound skin thickness measurements and a clinical assessment of bruising in 68 patients receiving long-term oral prednisolone (n = 15; 5-20 mg/d), high-dose inhaled beclomethasone dipropionate (n = 21; 1-2.5 mg/d), or low-dose inhaled beclomethasone dipropionate (n = 15; 0.2-0.8 mg/d) and in control subjects. The prevalence of bruising was 12% in controls, 33% in patients taking low-dose inhaled beclomethasone, 48% in patients taking high-dose inhaled beclomethasone, and 80% in patients taking prednisolone. Compared with controls, the measured skin thickness was 28% to 33% less in patients taking prednisolone and 15 to 19% less in patients taking high-dose beclomethasone, but no significant difference was seen in patients taking low-dose beclomethasone. The results of this study were strengthened in that patients receiving low-dose beclomethasone had not received long-term high-dose beclomethasone or prednisolone therapy, whereas the patients receiving high-dose beclomethasone had never received long-term prednisolone treatment.

In a questionnaire-based survey, Mak et al. reported on bruising tendency in a group of 202 asthmatic patients taking inhaled corticosteroids compared with an age- and sex-matched group of asthmatic patients not taking inhaled corticosteroids. The prevalence of bruising was significantly greater in the patients using inhaled corticosteroids, although there was a particular tendency in older men receiving high-dose therapy. Roy et al. studied 100 adult asthmatic patients taking high doses of inhaled beclomethasone dipropionate or budesonide (0.8-2 mg/d) for at least 3 months compared with 100 age- and sex-matched non-asthmatic controls. Bruising was assessed using questionnaire and skin examination, and there was also a concomitant evaluation of 24-hour urinary cortisol excretion. The prevalence of bruising in asthmatic patients was 71% and 48% by questionnaire and examination, respectively, compared with a prevalence of 32% and 48%, respectively, for controls. There was a greater likelihood of skin bruising developing in older women. Furthermore, a higher number of bruising lesions on direct examination was associated with lower levels of urinary cortisol excretion. Comparable data on skin bruising are not available for the higher-potency inhaled corticosteroids such as fluticasone, although one might expect from first principles that bruising would occur at lower doses than with beclomethasone or budesonide.

The presence of skin bruising can be considered a visible marker of the adverse effects of corticosteroids on collagen turnover in connective tissue, and serial skin examinations therefore can be used to monitor potential systemic adverse effects in patients taking high-dose therapy. However, it is unclear whether early susceptibility to skin bruising relates to effects on collagen in other systemic tissues such as bone, and so the absence of skin bruising cannot be taken as a guide to the safety of a given dose of inhaled corticosteroid. Nonetheless, the presence of bruising points to the possibility of systemic effects developing elsewhere in bodily tissues.

There is no doubt that, compared with long-term oral prednisolone maintenance therapy, the use of inhaled corticosteroids has improved the benefit-risk ratio for the preventive treatment of asthma vastly. However, the trend toward the earlier use of inhaled corticosteroids, particularly in children, makes it even more important to appraise critically their potential for producing systemic adverse effects during long-term administration.

Meta-analysis reveals fluticasone propionate to exhibit greater dose-related adrenal suppression than other available inhaled corticosteroids, particularly at doses above 0.8 mg/d. These differences cannot be accounted for by enhanced potency alone when comparing therapeutically equivalent doses, and probably represent the particular pharmacokinetic properties of fluticasone. There is considerable interindividual susceptibility to systemic effects of inhaled corticosteroids, so that it is difficult to predict whether systemic effects will develop in an individual at a given dose of inhaled corticosteroids.

The potential for systemic adverse effects with high-dose inhaled corticosteroids will become increasingly relevant, as there are now effective alternative nonsteroidal therapies, including the long-acting β2-agonists, theophyllines, and antileukotrienes, that may permit the use of a lower dose of inhaled corticosteroid when used as additive therapy. For the small proportion of patients who are dependent on high-dose inhaled corticosteroid therapy, it would seem prudent to perform regular annual or biennial checks for evidence of systemic adverse effects on skin, bone, eye, adrenal gland, and growth. The most rational approach is to minimize the potential systemic burden by always trying to taper to the lowest effective maintenance dose of inhaled corticosteroid, to achieve optimal long-term asthma control and quality of life.

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