

Limitations of short-term studies in predicting long-term adverse effects of inhaled corticosteroids

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This paper examines the value of short-term studies in predicting long-term, clinically relevant adverse effects of inhaled corticosteroids (ICS) in children with asthma. Increasing use of ICS in younger and less severely affected children with asthma justifies concern about long-term adverse effects. For each system potentially affected by ICS, short-term and sensitive studies have limited value in predicting clinically relevant effects, even when correlations are highly statistically significant. This is due to inherent limitations of the short-term tests utilized and normal physiologic variations in systems being studied. Specific limitations include:

- 1) poor distinction between systemic presence of ICS and adverse systemic effects (e.g., integrated plasma cortisol)
- 2) lack of data validating the connection between test results and the end point in question (bone markers to predict growth and fracture risk)
- 3) sensitivity confounded by normal physiologic variation (knemo-metry to predict long-term growth).

Consequently, predicting *clinically relevant long-term effects* from short-term studies detecting *physiologic perturbations* remains a challenge. Positive predictive value is improved by well-designed intermediate-term (>12 months) studies utilizing dynamic hypothalamic-pituitary-adrenal (HPA) axis testing, dual x-ray absorptiometry (DXA) scanning, or precise stadiometry. Ultimately, however, long-term studies are required to assess long-term risks, and the reliability of short-term assessments in predicting them.

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Inhaled corticosteroids (ICS) are being prescribed for younger children, with greater consistency of administration, and for longer periods of time (1). Appropriately, concern about potential long-term adverse effects of ICS treatment persists. Numerous studies document the effects of systemically absorbed ICS on the hypothalamic-pituitary-adrenal (HPA) axis, bone metabolism, and growth. Not surprisingly, there continues to be hope that the findings of short-term studies, which are relatively easy to conduct and to control, will predict long-term adverse effects of ICS.

Unfortunately, the high sensitivity of the techniques employed in short-term studies often compromises positive predictive value for the adverse effect in question. Thus, while short-term studies effectively identify systemic effects of ICS, and even shed light on underlying mechanisms, they fail to predict accurately the long-term consequences of these effects. Increasing duration of study leads to improved positive predictive value for virtually all the clinically relevant adverse effects of ICS. A role for short-term tests of ICS systemic effects to screen for individuals requiring more intensive safety monitoring remains to be defined.

Test characteristics

The validity of a test to detect the presence or absence of an adverse drug effect can be judged by its sensitivity and specificity. Sensitivity, the true positive rate, is the probability that a person demonstrating an adverse effect will have a positive test result. Sensitivity approaching 100% avoids underdiagnosis, but also results in greater false-positive rates. Specificity, the true negative rate, is the probability that a person not demonstrating the adverse effect will have a negative test result. Of greater value to the clinician is the *positive predictive value*, which, for purposes of our discussion, indicates the proportion of individuals who ultimately manifest the clinically relevant adverse effect after a positive short-term test. The lower the positive predictive value, the greater the number of patients mistakenly identified as at risk of an adverse effect.

Optimally, short-term tests of ICS effects would have high sensitivity for detecting changes *known to lead to* a clinically relevant adverse effect, accompanied by a high positive predictive value to minimize false-positive predictions of treatment complications and unnecessary discontinuation of effective therapy. Fulfillment of these criteria by tests and techniques commonly used in short-term studies of ICS is diminished by the following:

- 1) poor distinction between systemic presence of ICS and clinically important systemic effects (e.g., integrated plasma cortisol)
- 2) lack of data connecting test result to the end point in question (bone markers to predict deficient mineral accretion or fracture risk)
- 3) sensitivity confounded by normal physiologic variation (knemometry to predict long-term growth).

Systemic drug presence vs adverse effect: HPA axis

The challenge of distinguishing detectable ICS-induced physiologic perturbations from clinically important adverse effects is particularly relevant to the HPA axis. Complications of glucocorticoid (GC) therapy occur when total GC exposure is greater than normal and/or the pattern of exposure is significantly altered from normal diurnal variation. Consequently, *replacement* of endogenous GC effects by systemically absorbed IC does not necessarily mean that effects of GC excess will occur.

Various tests of adrenal function reflect distinct aspects of HPA axis integrity (Table 1) (2). Urinary free cortisol excretion or area-under-the curve (AUC) 12- or 24-h plasma cortisol concentrations are very sensitive measures of endogenous cortisol production, which can be proportionately decreased by the presence of *any* systemically absorbed ICS. Consequently, statistically significant suppression of endogenous cortisol production is necessary, but frequently not sufficient, for development of clinically important HPA axis suppression. After bedtime administration of 200 µg of either beclomethasone dipropionate (BDP) or budesonide (BUD) to children with asthma (3), the nocturnal rise in cortisol is delayed (reflecting blunting of the early nocturnal ACTH surge) and AUC cortisol secretion reduced. On the other hand, after temporary suppression, cortisol levels rise to normal morning levels, indicating preservation of the diurnal rhythm of the HPA axis. Thus, while systemic presence of IC is demonstrated by AUC analysis, the predictive value of this finding for clinically important HPA axis suppression is likely to be low (Fig. 1).

Short-term studies of HPA axis function do allow prompt comparisons between the systemic “cortisol substitution” effects of various ICS (4). Reflecting differences in receptor binding affinity and other pharmacokinetic attributes, more potent medications (e.g., fluticasone dipropionate [FP]) show greater suppression of endogenous cortisol than less potent

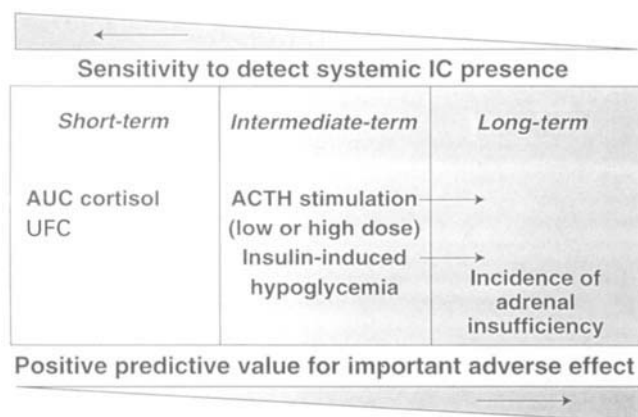


Figure 1. Short-, intermediate-, and long-term tests of effects of ICS on HPA axis. Sensitivity for detecting systemic presence of ICS is greatest with AUC cortisol measurement; positive predictive value for risk of adrenal insufficiency is increased by dynamic tests of adrenal responsiveness. UFC: urinary free cortisol.

ones (BDP or BUD) when compared microgram-for-microgram. Such comparisons must, however, also consider *clinically equivalent* doses of ICS and account for delivery-device differences in lung drug deposition. Until the issue of equivalent dosage/device regimens is resolved, short-term microgram-for-microgram comparisons of ICS add little to the clinician's ability to assess risk vs benefit of a particular drug.

Failure to connect short-term results to long-term effect: *bone metabolism*

Some studies of adults treated with ICS, for the most part in high doses, reveal reduced total bone mass and reduced bone mineral density (BMD) (5), although excessive osteoporosis or fracture rates have not been reported in patients who have been treated with long-term ICS alone. An adverse effect of ICS on bone mineral accretion would be of particular concern in growing children, particularly during adolescence. The finding that levels of osteocalcin (6), serum markers of type I and type III collagen formation, and serum markers of type I collagen degradation (7, 8) can be affected by high-dose ICS treatment suggests that ICS have the potential to affect adversely bone growth, BMD, and eventual fracture risk, although the existing long-term evidence suggests that this is not the case (9, 10).

Relationships between serum markers of bone metabolism and growth in ICS-treated patients are inconsistent. In children without asthma, the only prospective study of growth and serum osteocalcin showed no significant relationship (11). Studies of BDP- (12) and FP-treated (7) children found osteocalcin to be a poor marker for decreased growth (measured

by stadiometry) associated with the use of ICS. Growth suppression (measured by knemometry) in children receiving 400–800 µg/day BDP was associated with reductions in markers of collagen degradation skin and loose connective-tissue collagen synthesis, but not in the major collagen in bone (i.e., type I procollagen) (7). While evidence supports IC-mediated effects on collagen metabolism as a mechanism for growth suppression (8), the value of biochemical markers in predicting growth remains limited: even a highly statistically significant correlation (e.g., 0.5) indicates that only a low percentage of the variation in growth may be explained by the marker.

Most of the information on the effects of ICS on bone turnover has been obtained in adults treated with moderate-to-high doses. Measurements of BMD in children treated with BDP or BUD have been similar to those in untreated children (13). Markers of bone resorption (e.g., urinary deoxypyridinoline) are unaffected by moderate-dose BDP treatment, even in children who exhibit growth suppression (14). On the other hand, serum osteocalcin levels can be reduced in BDP-treated children with normal BMD, suggesting that asthma per se might reduce osteocalcin independently of corticosteroid effect (13).

Since normal BMD and normal final height have (thus far) been characteristic of children treated with ICS (9, 10, 15), there is, as yet, no valid association between short-term bone metabolism markers and a clinically important end point. Until there is documentation of the long-term effects of ICS on BMD, changes, for instance, in biochemical markers are likely to overestimate clinical risk. Studies of elderly patients have only recently identified markers (e.g., urinary type I collagen N-telopeptide) which efficiently distinguish between normal, osteopenic, and osteoporotic BMD *already present* (16). No studies have shown prospectively that bone markers evaluated early in the course of IC treatment predict subsequent normality or adverse changes in BMD. Even direct measurement of BMD by either quantitative microdensitometry or dual x-ray absorptiometry (DXA), while capable of predicting risk of fracture, cannot reliably identify individual people who will have a fracture (17). In summary, short-term markers of bone turnover sensitively identify and even provide insights into mechanisms of the effect of ICS on bone, but have not been shown to predict consequences of this effect (Fig. 2).

Confounding by normal physiologic variations: knemometry

Childhood growth is complicated by changing factors regulating growth, normal variation in the tempo of long-

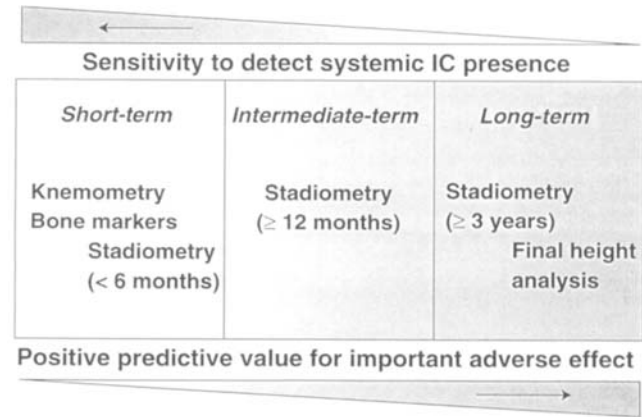


Figure 2. Short-, intermediate-, and long-term tests of effects of ICS on bone. Markers of bone turnover have high sensitivity for detecting ICS systemic effect, but unverified positive predictive value for fracture risk or poor growth.

term growth and pubertal development, and normal short-term (often abrupt) changes in growth rate. The difficulty of conducting controlled studies of ICS effects on long-term growth prompted interest in short-term (i.e., < 6 months) studies using knemometry (measurement of lower leg growth) which could utilize: 1) very short observation periods; 2) controlled, randomized, double-blind conditions; 3) crossover trials (18). Knemometry studies have generally shown growth suppression during treatment with BUD (by metered-dose inhaler) at doses of >400 $\mu\text{g}/\text{d}$, with BDP at doses of ≥ 400 $\mu\text{g}/\text{d}$, and with BUD (Turbuhaler) or FP at 400 $\mu\text{g}/\text{day}$ (19).

Unfortunately, short-term lower leg-growth rates cannot be extrapolated to intermediate- or long-term growth. Childhood growth normally occurs in spurts, interspersed with periods during which essentially no growth occurs (20). The precision of knemometry detects this irregular pattern which, when combined with a focus on lower-leg growth only, actually becomes a liability in the prediction of overall linear body growth. Even when measurements are carried out over 4 months, 6-month growth velocity is predicted only within 28.8% [mean ± 2 SD]], and correlations of growth of the lower leg with total height over 6 months are indifferent. Shorter time intervals produce even poorer predictions (21).

The inability of knemometry to predict statural growth has been illustrated in one study of children treated with ICS (22). In addition to normal variations in short-term growth, this result might also reflect differences in the consistency of ICS dose between short- and longer-term studies (23). Recent well-designed and tightly monitored prospective studies reveal 12-month growth suppression

during uninterrupted daily treatment with BDP 400 $\mu\text{g}/\text{day}$, a dose known to cause detectable growth slowing in knemometry studies (12, 24). Prospective studies which combine early application of knemometry with careful stadiometry measurements and close monitoring of consistent-dose IC administration over a period of ≥ 12 months are needed to evaluate further the predictive value of knemometry measurements in IC-treated children. (Fig. 3).

The sensitivity of knemometry might allow the exclusion of risk for growth suppression by ICS based upon short-term screening for the *absence* of slowed lower-leg growth (19). However, reliable exclusion of an adverse effect based upon a negative test requires high specificity as well as sensitivity, and both aspects are compromised by normal short-term variations in growth. If a child begins ICS treatment during a time of normally slow or absent growth, knemometry measurements in subsequent weeks would not detect a slowing of growth attributable to ICS. Thus, for individual patients, knemometry studies have limitations in predicting both the presence and absence of long-term effects of ICS on growth. On the other hand, in the evaluation of study groups, knemometry appears to be useful in comparing differences in systemic activity between drugs and may be useful in identifying generally safe doses of ICS. Corroboration of short-term predictions of safe ICS doses with results of intermediate- and long-term studies is needed to strengthen the clinical value of knemometry studies.

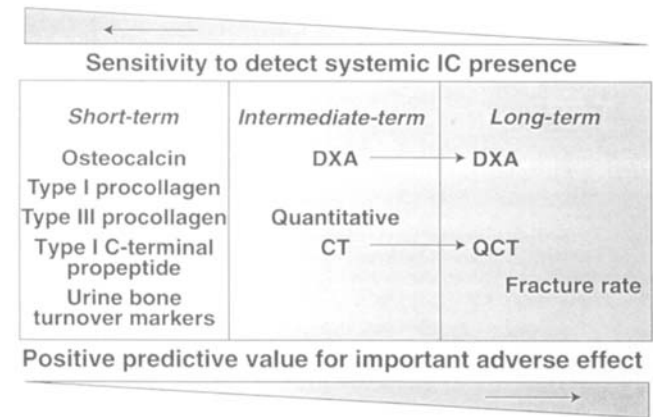


Figure 3. Short-, intermediate-, and long-term tests of effects of ICS on growth. Highly sensitive knemometry is poor predictor of long-term growth, which is more accurately assessed by intermediate- or long-term stadiometry.

Conclusions: the added value of intermediate-term studies

Several tests with high sensitivity for detecting systemic effects of ICS have been employed in short-term studies assessing the risks of IC treatment. The positive predictive value of these tests for the development of clinically important adverse effects is low. As illustrated above, AUC plasma cortisol profiles and urinary free-cortisol collections accurately indicate systemic presence of absorbed ICS, but do not predict the loss of HPA axis rhythmicity. Markers of bone turnover can be correlated with changes in BMD (in adults) and growth rate, but have not been shown to predict either poor mineralization or growth in children treated with ICS. Knemometry sensitively assesses growth of the lower leg, but is confounded by normal week-to-week variations in childhood growth and correlates poorly with total body growth. Consequently, while short-term tests have value in detecting the presence and even the mechanism of a systemic effect of absorbed ICS, they do not, thus far, predict the consequences of these effects.

Long-term studies of sufficient duration to evaluate actual occurrence of the potential clinically important adverse effects of ICS (episodes of adrenal insufficiency, reduced final adult height, increased fracture rate) are ultimately required to prove the risks of long-term ICS treatment. However, the time required for such studies inevitably introduces multiple confounding factors, particularly in a

study group of patients with a chronic disease of fluctuating severity. For effects on linear growth and bone metabolism, the many years required to assess end points can even overlap periods of profound change in prevailing strategies for disease management.

Although intermediate-term studies rarely provide information about the occurrence of clinically important adverse effects of ICS, they can evaluate physiologic changes *directly connected* (e.g., total body growth rate measured by careful stadiometry; diminished BMD by DXA) to the clinically important adverse effect. This offers an important advantage over short-term studies, in which reliance is placed on measurement of markers thought to correlate with the effect. Accordingly, the duration of adequate intermediate-term safety studies for ICS is defined by the time required to detect reliably this physiologic change; for example, estimated durations are of ≥ 3 months to demonstrate development of adrenal atrophy and diminished response to exogenous ACTH stimulation, of ≥ 12 months for the documentation of slowed growth in total height, and perhaps of ≥ 24 months for changes in BMD. Controlled studies of this duration are difficult to conduct, but recent efforts indicate that these obstacles can be overcome (25). Consequently, well-designed intermediate-term studies of the response of the HPA axis to stimuli, changes in BMD, or statural growth, which combine controlled study feasibility with improved positive predictive value, provide the best practical opportunity to increase knowledge about the long-term risks of ICS.

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