

Assessing the therapeutic index of inhaled corticosteroids in children: Is knemometry the answer?

H. William Kelly, PharmD Albuquerque, NM

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Since the introduction of topical inhaled corticosteroids (ICSs) for the treatment of asthma decades ago, there have been concerns about potential risks from systemic activity.¹ This has been particularly true regarding ICS use in young children, in whom growth and development represent additional issues.² Despite the ongoing development over the years of newer ICS molecules with pharmacokinetic properties that improve the therapeutic index (ratio of topical activity to systemic activity), such as decreased oral bioavailability, rapid systemic clearance, and lung retention (Fig 1), all ICSs still work by stimulating glucocorticoid receptors, which are found throughout the body. Thus, given in high enough doses, the risks of systemic effects exist with any ICSs.

This has been brought into sharp relief by a recent report that two thirds of 143 children attending an allergy specialty clinic had evidence of hypothalamic-pituitary-adrenal (HPA) axis dysfunction that was correlated with ICS plus nasal corticosteroid daily dose per square meter.³ Currently, the US Food and Drug Administration requires a measure of basal cortisol excretion and year-long growth studies for approval of ICSs in children 4 to 11 years of age because effects on growth occur in the absence of effects on basal cortisol excretion.⁴ In addition, measures of basal cortisol excretion (24-hour serum concentration area under the curve, 24-hour urinary free cortisol [UFC] excretion, or 12-hour overnight UFC excretion, the latter 2 corrected for creatinine excretion) are approved for comparing relative systemic effects of different ICSs or the effect produced by device differences.

In this issue of the *Journal*, Chawes et al⁵ present the results from a comparative study in children 5 to 12 years old receiving 200 µg/d extrafine-particle beclomethasone dipropionate (BDP) for 2 weeks administered with and without a long-acting β₂ agonist through a metered-dose inhaler (MDI) and valved holding chamber. Lower-leg growth rate (LLGR) measured by means of knemometry was lower after each 2 weeks of active treatment,

whereas there were no differences in the 24-hour UFC measures for detecting systemic activity. In addition, the authors found that by using more measures of each leg than is standard, variability in the test because of investigator, season, child's age, and sex was not significant, improving the precision of the knemometry. Thus the authors concluded that knemometry was more sensitive and should be used preferentially over 24 hours of UFC for comparing relative systemic activity of the various ICSs and delivery devices in children. This study was meticulously performed; however, the variances between patients, as well as in the ICS effects, were still wide, and the mean baseline LLGR was 0.55 mm/wk (SD, 0.33 mm/wk), with a few patients with negative values. The effect of the ICS was a mean decrease of 0.27 mm/wk (95% CI, 0.05-0.48 mm/wk) by using the newer technique. The results highlight one of the traits of sensitive measures: a (notably shared by measures of baseline cortisol secretion) high interpatient variability and response.^{3,6}

Numerous studies including both knemometry and 24-hour UFC have been published to date, as indicated by Chawes et al.⁵ Most show similar outcomes with knemometry, indicating systemic activity of ICSs but not UFC, but a few do not, likely a result of the higher doses used in those studies.^{7,8} It would be easy to critically compare these various studies and try to decide the best measure for assessing the systemic effect side of the therapeutic index for the various ICSs but that would obscure a more basic issue: Do sensitive measures of systemic activity reflect or predict clinically relevant risks to the children receiving ICS therapy? Current evidence demonstrates neither a high predictive quality of knemometry for 1-year growth velocity nor UFC measures for HPA axis suppression.^{3,6} Although 1 trial demonstrated a strong correlation between every 8 weeks of knemometry and 52-week growth velocity, it was performed with a dose of budesonide (BUD) administered by means of dry powder inhaler (DPI), which is known to produce a significant decrease in yearly growth velocity.⁹ It has been posited that an LLGR suppression of 40% or greater would predict an effect on yearly growth velocity, but this has not been rigorously tested in prospective trials.⁶

If a test is to distinguish between various ICSs and delivery devices, it should demonstrate clear dose responsiveness. In the few studies incorporating doubling doses of the ICSs administered with the same device, dose responsiveness was not apparent for either knemometry or 24-hour UFC.^{7,8} In a comparison of 200- and 400-µg daily doses of fluticasone propionate (FP) and BUD, both administered through a DPI, no effect on LLGR was seen with FP, and a significant decrease was seen in 24-hour UFC that was the same for each dose.⁷ A significant decrease in LLGR and UFC was found for the 400-µg dose of BUD, but no differences were found between FP and BUD for either daily dose. A comparison between 200 µg/d extrafine-particle MDI BDP and standard-particle MDI BDP used 2 doses of the latter:

From the Department of Pediatrics and College of Pharmacy, University of New Mexico Health Sciences Center.

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Corresponding author: H. William Kelly, PharmD, Department of Pediatrics and College of Pharmacy, University of New Mexico Health Sciences Center, 9828 Guadalupe Trail NW, Albuquerque, NM 87114. E-mail: hwkelly@unm.edu.

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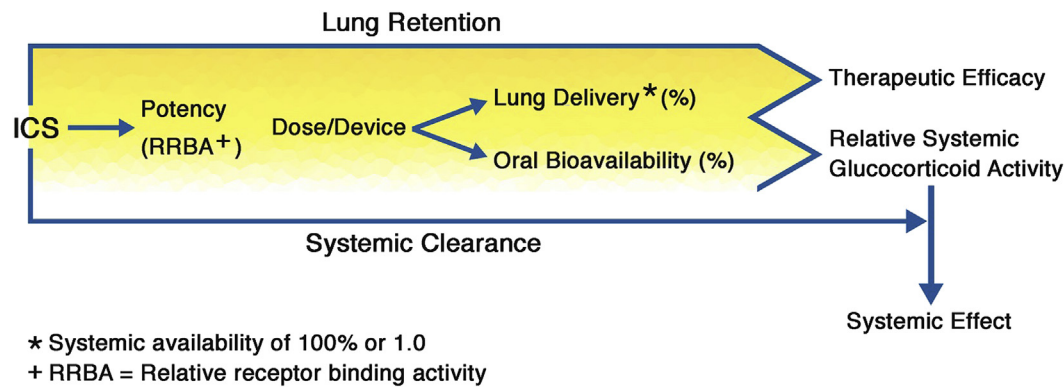


FIG 1. Determinates of the ICS therapeutic index.

200 and 400 $\mu\text{g}/\text{d}$.⁸ Significant suppression from baseline in LLGR was recorded for all doses in the range of 80% (near maximum suppression) without differences between doses or devices. Significant reductions from baseline were also reported for UFC values without dose or device differences.

Some of the difficulties we have had in determining comparative therapeutic indices between various ICSs include insensitivity of therapeutic efficacy (2-fold changes in dose rarely showing clinically relevant differences), clearly establishing appropriate systemic effects, and failure to consider all aspects (Fig 1) to determine both dose to lung and systemic circulation. Researchers are often faced with having to use regulatory agency–approved doses because funding often comes from the ICS manufacturers, making dose-response studies difficult to perform. Recommended doses from guidelines are based on comparative clinical trials of efficacy and not analysis of systemic activity.^{1,10} Although we think of those doses as equivalent, they are only within the 2-fold difference in potency or delivery. However, systemic activity differences can be detected with carefully designed comparative trials, as has been shown with FP administered through a DPI versus MDI plus valved holding chamber.¹⁰

A new approach to designing comparative trials of systemic activity that might improve efficiency in determining the therapeutic index would be to compare the drugs and devices in doses that would be expected to result in significant differences in relative systemic glucocorticoid activity (RSGA; Fig 1), which takes into account relative receptor-binding affinity, as well as dosing and bioavailability differences. Using RSGA will also begin to help us determine the relative effect of lung retention and systemic clearance on therapeutic index. Daily but not cumulative ICS doses are predictive of both annual growth suppression and HPA axis dysfunction.^{3,4} Therefore the RSGA is calculated from the product of the daily dose, relative receptor binding affinity, and systemic bioavailability (oral plus lung). For example, based on the RSGA of 4 approved products in children and the resulting mean decrease in annual growth, it is easy to see why there are differences in the outcomes of these studies as follows:

- (1) BDP MDI 100 $\mu\text{g}/\text{d} \times 13.5 \times 0.70 = 756 \rightarrow -1.1 \text{ cm/y}$;
- (2) BUD DPI 200 $\mu\text{g}/\text{d} \times 9.4 \times 0.35 = 658 \rightarrow -0.45 \text{ cm/y}$;
- (3) FP DPI 100 $\mu\text{g}/\text{d} \times 18.0 \times 0.16 = 270 \rightarrow -0.21 \text{ cm/y}$;
and
- (4) Flunisolide MDI 160 $\mu\text{g}/\text{d} \times 1.8 \times 0.80 = 230 \rightarrow -0.17 \text{ cm/y}$.

Returning to the original question of whether knemometry is the answer to improving our assessments of the therapeutic index, knemometry is noninvasive and requires only a short treatment interval but currently lacks predictive quality for clinically significant systemic adverse effects on annual growth or HPA axis function. If you want the most sensitive indicator of systemic activity, this study and others suggest knemometry is it. Significantly more research is needed to inform us of its utility for comparing ICS products, doses, and devices.

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