Do Inhaled Corticosteroids Really Affect Growth?

David P. Skoner, MD
Director, Division of Allergy, Asthma & Immunology, Department of Medicine, Allegheny General Hospital, Pittsburgh, Pennsylvania. Professor of Medicine, Temple University. Professor of Pediatrics, West Virginia University.

LEARNING OBJECTIVES

1) Illustrate sources of systemic bioavailability for inhaled corticosteroids.
2) Describe the effects of inhaled corticosteroids on the growth of children with asthma.
3) Review methods to minimize and manage the risk of growth suppression.
Evolution of Asthma Management, Cincinnati Children’s Hospital, 1981

- Intern on 3 South, admitted 5 children with asthma by 1am
- Chief Resident makes rounds at 1:30am and asks two questions:
  - 1) Can we get the theophylline levels a little higher?
  - 2) How many did you manage to keep off “steroids”?
- The change from then until now is dramatic, since current guidelines have ICS as the foundation, and theophylline is rarely used.


Adherence rates are also very low, and one reason is steroid phobia!

Compared to non-Hispanic white children, lower use among non-Hispanic black (aOR = 0.5) and Mexican American (aOR = 0.6) children.

* Included inhaled corticosteroids, leukotriene receptor antagonists, long-acting β-agonists, mast-cell stabilizers, and methylxanthines.


Systemic Bioavailability of ICS

Potential impact on growth
Potential Interaction Between Growth Axis and Nocturnal INS or ICS Administration

Interaction of childhood growth and HPA axes. The commencement of nocturnal pulsatile growth hormone secretion normally coincides with the nadir in plasma cortisol concentrations. Consequently, the administration and absorption of inhaled corticosteroids at bedtime could theoretically have a disproportionate suppressing influence on growth, compared with early morning dosing. GH: growth hormone.

Safety of ICS in Children – Growth Effect?
• Is it real and dose-related?
• How large is it?
• Do all ICS affect growth equally?
• What is the FDA’s position?
• Does the effect change our approach to therapy?

Phases of Childhood Growth

Figure 1. Timeline of Growth Studies in Children with Asthma

Expert Panel Report (EPR)
Guidelines for the Diagnosis and Management of Asthma issued, recommending ICS as preferred therapy

FDA issues draft guidance for industry on conduct of ICS growth studies in children

Numerous growth studies published (inhaled and intranasal steroids)

FDA convenes meeting and recommends class labeling for all inhaled and intranasal steroids regarding possible growth suppression

First study utilizing criteria in FDA guidance published (montelukast growth study)

Second study utilizing criteria in FDA guidance published (ciclesonide growth study)


METHODS OF MEASURING GROWTH

Stadiometry (Harpenden Model)
Knemometry

Both Sensitive Devices

DOSE-RESPONSE EFFECT ON GROWTH

CFC Formulations

Am J Respir Crit Care Med 1998;158:213-219
No Significant Difference in Mean Height After 1 Year of Treatment

Open-label, randomized study of 300 children ages 5-11 yrs with asthma well-controlled on ICS (BDP or BUD). 1:3 randomization to continue CFC-BDP+S at approximately the same dose or switch to HFA-BDP at half the dose.

What about HFA formulations?

Mean change from baseline in height (cm)


No Significant Difference in Mean Height After 1 Year of Treatment

One-year trial of growth in asthmatic children including those receiving higher-than-recommended BDP doses.

What about HFA formulations?

Mean growth velocity from Day 1 to Month 12 (cm/year)

* Small n values at higher doses

Pediatrics 2002;109(6):e92(1-10)

Most Children Remained in Same Height Centile After 1 Year of HFA-BDP Treatment

Note interindividual response variation

Long-term Effects of Fluticasone Propionate (FP) on Growth


Design: Double-blind, randomized, placebo-controlled, multicenter

Population: 325 prepubescent children with persistent asthma

Treatment: FP powder 100 μg or 200 μg via Rotadisk™ or placebo for 1 year

Growth Velocity:
- Placebo: 6.10 cm/yr ± 0.17
- FP 100 μg: 5.91 cm/yr ± 0.16
- FP 200 μg: 5.67 cm/yr ± 0.13

Inhaled FP: Summary

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Control 50 mcg</th>
<th>100 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 3</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>≤ 10</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>≤ 25</td>
<td>18%</td>
<td>21%</td>
</tr>
<tr>
<td>≤ 50</td>
<td>35%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Comparison of the Fluticasone ICS/INCS Formulations

<table>
<thead>
<tr>
<th>Name</th>
<th>Dosage (mcg/puff)</th>
<th>Systemic Bioavailability</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS Rotadisk</td>
<td>50,100,250</td>
<td>13.5%</td>
<td></td>
</tr>
<tr>
<td>ICS pMDI</td>
<td>44,110,220</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>ICS Diskus</td>
<td>100,250,500</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Intranasal</td>
<td>50</td>
<td>&lt;2%</td>
<td></td>
</tr>
</tbody>
</table>

* per package insert, 2001 PDR
† used in one-year growth study
‡ For asthma, healthy volunteers, dose delivered from actuator, primarily reflects lung delivery
§ plus 50mcg salmeterol/puff
Growth velocity was similar in the two study groups at the end of treatment

Growth Velocity
Nebulized Budesonide vs Conventional Asthma Therapy

Mean growth velocity for 527 children treated with nebulized budesonide (BUD) or conventional asthma therapy (CAT) for 52 weeks of treatment in children aged 6 months to 8 years.

Mildest patients may be the most susceptible to the growth effects of ICS.

Effects of Inhaled Mometasone Furoate on Growth Velocity and Adrenal Function: A Placebo-Controlled Trial in Children 4–9 Years Old with Mild Persistent Asthma

Multicenter, randomized, double-blind, placebo-controlled, parallel-group study

Effects of Inhaled Mometasone Furoate on Growth Velocity and Adrenal Function: A Placebo-Controlled Trial in Children 4–9 Years Old with Mild Persistent Asthma


Effect of Inhaled Triamcinolone Acetonide (TAA) on the Growth of Children with Moderate Asthma (Real-World Study)

Mean 1-year growth difference (final height minus baseline height); P-value is comparison vs. normal.


INDIVIDUAL GROWTH DATA FROM “REAL WORLD” STUDY

Figure 3. Growth velocity distribution in normal and moderately severe asthmatics.

ICS Labeling Resulting from FDA Meeting
July 1998

Prescribing information for:

Beclomethasone

Budesonide

Fluticasone

Adapted from QVAR® prescribing information, 3M, October 2003; Pulmicort® prescribing information, AstraZeneca, December 2003; Flovent® prescribing information, GlaxoSmithKline, March 2004.

Country responsibility to make consistent with local labeling.

Drug Inhaler Rx (µg/day)

<table>
<thead>
<tr>
<th></th>
<th>BDP without spacer</th>
<th>BDP with spacer</th>
<th>BUD-MDI</th>
<th>BUD-dry powder</th>
<th>DP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose</td>
<td>200</td>
<td>350</td>
<td>500</td>
<td>600</td>
<td>800</td>
</tr>
<tr>
<td>Medium-dose</td>
<td>200</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>800</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>800</td>
</tr>
</tbody>
</table>

Benefits/risk

Adverse effect

Clinical relevance

Effect of ICS Dosage on Therapeutic and Systemic Corticosteroid Effects

Growth and Inhaled Steroids

Inhibition of lower leg growth using knemometry
2001 FDA Guidelines for Evaluation of the Effects of Inhaled Corticosteroids on Growth

**Population**
- Pre-pubertal
- Mild, persistent asthma
- Comparable baseline demographics

**Study design**
- Primary: Regression analysis of growth velocity
- Total length of 95% CI ≤ 0.5 cm
- Secondary: Shift analysis in growth velocity percentile; analysis of growth velocity percentiles; growth velocity during follow-up
- At least 1 year treatment period
- Untreated control group
- Baseline growth velocity data (at least 16 weeks)
- Follow-up period (at least 8 weeks)
- Repeat stadiometer measurements
- Cortisol measurements
- Pulmonary function tests

**Analysis**
- Placebo
- Montelukast 5 mg once daily (n=120)
- Placebo (n=121)
- Beclomethasone 200 µg twice daily (n=119)

Period I
- Single-blind run-in
- Beclomethasone 200 µg twice daily (n=119)
- Placebo (n=121)

Period II
- Double-blind treatment*
- Montelukast 5 mg once daily (n=120)

16 weeks 0 56 weeks

*As-needed short-acting beta2-agonist use was permitted for symptom control or pre-exercise prophylaxis; one oral corticosteroid rescue was permitted during run-in and up to four during double-blind treatment.


Linear Growth Stadiometry Study in Prepubertal Asthmatic Children

**Design**

- **Period I**
  - Single-blind run-in
- **Period II**
  - Double-blind treatment*

- Montelukast 5 mg once daily (n=120)
- Beclomethasone 200 µg twice daily (n=119)
- Placebo (n=121)

16 weeks 0 56 weeks

*As-needed short-acting beta2-agonist use was permitted for symptom control or pre-exercise prophylaxis; one oral corticosteroid rescue was permitted during run-in and up to four during double-blind treatment.


Linear Growth Stadiometry Study in Prepubertal Asthmatic Children Aged 6–9 Years

6–9 Years Is an Appropriate Age Range for a Linear Growth Study

- The 2–3 years prior to puberty are likely to be the most susceptible to growth suppression by asthma drugs

**The Effect of Montelukast and Beclomethasone on the Rate of Linear Growth in Children**

Change in Height (cm) from Randomization Visit (Baseline) to Week 56 (Treatment Group Mean ± Standard Error† of the Mean)

† The standard errors of the treatment group means in change height are too small to be visible on the plot.

Beclomethasone ex-valve dose (400 µg) is equal to 336 µg ex-activator dose.

**Linear Growth And Bone Maturation Are Unaffected By 1 Year Of Therapy With Inhaled Flunisolide Hydrofluoroalkane In Prepubescent Children With Mild Persistent Asthma: A Randomized, Double-blind, Placebo-controlled Trial**

Prepubescent (Tanner Stage 1) children (n=218) with mild persistent asthma ages 4 to 10 years were evaluated. After a 2-week run-in, subjects were randomized (1:1) to 2 puffs flunisolide HFA twice daily (85 g/puff) or placebo for 52 weeks. Height was assessed by stadiometry.

**Assessment of the Long-term Safety of Inhaled Ciclesonide on Growth in Children with Asthma**


**Linear Growth And Bone Maturation Are Unaffected By 1 Year Of Therapy With Inhaled Flunisolide Hydrofluoroalkane In Prepubescent Children With Mild Persistent Asthma: A Randomized, Double-blind, Placebo-controlled Trial**

Prepubescent (Tanner Stage 1) children (n=218) with mild persistent asthma ages 4 to 10 years were evaluated. After a 2-week run-in, subjects were randomized (1:1) to 2 puffs flunisolide HFA twice daily (85 g/puff) or placebo for 52 weeks. Height was assessed by stadiometry.

**Assessment of the Long-term Safety of Inhaled Ciclesonide on Growth in Children with Asthma**

Compliance

- Total number of puffs recorded in daily diary
- Definition of compliance on a given day: study medication taken per protocol (one puff in AM)
- Definition of compliance between study visits: 75% overall compliance and no consecutive missed doses of >5 days

<table>
<thead>
<tr>
<th>Compliance method</th>
<th>Placebo (n=221)</th>
<th>CIC 40 µg/day (n=221)</th>
<th>CIC 160 µg/day (n=219)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diary</td>
<td>99.1</td>
<td>93.7</td>
<td>96.8</td>
</tr>
<tr>
<td>Canister weight</td>
<td>79.6</td>
<td>81.9</td>
<td>80.4</td>
</tr>
</tbody>
</table>

What Might Have Enabled Conclusions To Be Drawn From This Study?

- A growth effect from one of the doses
- An HPA axis effect from either dose (none detected)
- Webcam proof of adherence (not done)
- Detection of ciclesonide in blood (not done)
- An effect on FEV1 (mild asthma, normal at baseline, montelukast allowed, primary growth [not efficacy] study)
What More Do We Need to Know About Growth Effects of ICS?

- Well-designed, long-term studies and impact on final adult height
- Intermittent vs. continuous therapy
- Genetic and environmental influences – at risk population
- Dose-response studies
- Comparative studies
- Combined intranasal and inhaled delivery
- Chronotherapy (optimal timing of a once-daily ICS dose)

The START Study: Growth in the Budesonide Group Minus That in the Placebo Group

Effects of Long-term Inhaled Budesonide on Adult Height in Children With Asthma


Overview of CAMP and CAMP Continuation Studies (CAMPCS)


CAMPCS: additional 4.8 yr. observation phase (n=941)

1,041 children aged 5 to 12 years with mild to moderate asthma, 4-6 yr. treatment phase

Budesonide 200 mcg twice daily (n=311)
Nedocromil sodium 8 mg twice daily (n=312)
Placebo (n=418)

Further Analysis of CAMP
Growth Velocity Varies with Developmental Stage

Height velocity for boys 2–19 years of age

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Height velocity (cm/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>7.5</td>
</tr>
<tr>
<td>6</td>
<td>7.0</td>
</tr>
<tr>
<td>7</td>
<td>6.5</td>
</tr>
<tr>
<td>8</td>
<td>6.0</td>
</tr>
<tr>
<td>9</td>
<td>5.5</td>
</tr>
<tr>
<td>10</td>
<td>5.0</td>
</tr>
<tr>
<td>11</td>
<td>4.5</td>
</tr>
<tr>
<td>12</td>
<td>4.0</td>
</tr>
<tr>
<td>13</td>
<td>3.5</td>
</tr>
<tr>
<td>14</td>
<td>3.0</td>
</tr>
<tr>
<td>15</td>
<td>2.5</td>
</tr>
<tr>
<td>16</td>
<td>2.0</td>
</tr>
<tr>
<td>17</td>
<td>1.5</td>
</tr>
<tr>
<td>18</td>
<td>1.0</td>
</tr>
<tr>
<td>19</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Growth Velocity with Budesonide—Lower in Year 1, Similar to Placebo in Years 2–4

All groups had similar growth velocity by the end of the treatment period.
Selected Patient Characteristics at CAMPCS Completion

<table>
<thead>
<tr>
<th>Treatment Group in CAMP</th>
<th>Budesonide n=284</th>
<th>Nedocromil n=277</th>
<th>Placebo n=380</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at end of trial, y</strong></td>
<td>13.4</td>
<td>13.2</td>
<td>13.3</td>
</tr>
<tr>
<td><strong>Age at end of posttrial (CAMPCS), y</strong></td>
<td>18.2</td>
<td>18.0</td>
<td>18.2</td>
</tr>
<tr>
<td><strong>Duration of posttrial, y (CAMPCS)</strong></td>
<td>4.8</td>
<td>4.9</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>% time on ICS during trial</strong></td>
<td>96.8a</td>
<td>4.1</td>
<td>18.0</td>
</tr>
<tr>
<td><strong>% time on ICS posttrial (CAMPCS)</strong></td>
<td>31.3</td>
<td>30.9</td>
<td>30.2</td>
</tr>
<tr>
<td><strong>Pre-BD FEV1% predicted at challenge</strong></td>
<td>93.7</td>
<td>93.5</td>
<td>92.7</td>
</tr>
<tr>
<td><strong>Post-BD FEV1% predicted at challenge</strong></td>
<td>100.1</td>
<td>100.2</td>
<td>99.3</td>
</tr>
</tbody>
</table>

*aStatistically significant difference in the CAMP budesonide treatment group vs placebo (P<0.001).
*bTime-dependent variables measured across all challenges. All other variables measured at baseline.

Patient Physical Growth at CAMPCS Completion

<table>
<thead>
<tr>
<th>Physical Growth</th>
<th>Budesonide n=284</th>
<th>Nedocromil n=277</th>
<th>Placebo n=380</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females, n</td>
<td>115</td>
<td>95</td>
<td>164</td>
</tr>
<tr>
<td>Height, cm</td>
<td>162.4</td>
<td>165.5</td>
<td>164.1</td>
</tr>
<tr>
<td>Females, n</td>
<td>98</td>
<td>84</td>
<td>141</td>
</tr>
<tr>
<td>Bone density, g/cm²</td>
<td>1.06</td>
<td>1.05</td>
<td>1.05</td>
</tr>
<tr>
<td>Males, n</td>
<td>169</td>
<td>182</td>
<td>216</td>
</tr>
<tr>
<td>Height, cm</td>
<td>179.2</td>
<td>178.0</td>
<td>175.0</td>
</tr>
<tr>
<td>Males, n</td>
<td>151</td>
<td>162</td>
<td>192</td>
</tr>
<tr>
<td>Bone density, g/cm²</td>
<td>1.02</td>
<td>1.01</td>
<td>1.02</td>
</tr>
</tbody>
</table>

*aStatistically significant difference in the CAMP budesonide treatment group vs placebo (P=0.001).
DAILY VERSUS AS-NEEDED INHALED CORTICOSTEROID FOR MILD PERSISTENT ASTHMA (THE HELSINKI EARLY INTERVENTION CHILDHOOD ASTHMA STUDY)

(176 children aged 5-10 years with newly detected asthma, FEV1 82-87% predicted)

Arch Dis Child 2008;93:654-659

Budesonide 400 μg bid for 2 weeks for exacerbations PRN

Use Of Beclomethasone Dipropionate (HFA) As Rescue Treatment For Children With Mild Persistent Asthma (TREXA): A Randomised, Double-blind, Placebo-controlled Trial


Combined: BDP-HFA 40 μg BID with BDP + albuterol as rescue;
Daily: BDP-HFA 40 μg BID with placebo + albuterol as rescue;
Rescue: Placebo BID with BDP + albuterol as rescue;
Placebo: Placebo BID with placebo + albuterol as rescue.

Rescue beclomethasone treatment was two puffs (80 μg) of BDP or placebo for each two puffs of albuterol (180 μg) needed for symptom relief.

Effects of ICS on Childhood Growth Using Stadiometry

(Mild disease, ≥ 1 yr, DB-PC, various ages)

BDP CFC=Becker et al., Annals Allergy Asthma Immunol. 2006;96:800-807
BDP HFA-Martinez et al., Lancet 2011; 377: 650–57 (not primary growth study)
BUD+CAMP study, NEJM 2003:349:1554-1563 (not primary growth study)
CIC=Skoner et al., Pediatrics. 2008;121:e1-14 (FDA: Conclusions cannot be drawn from this study because compliance could not be assured)
FP=Guilbert et al., NEJM. 2005;353:1895-1907 (not primary growth study)

LOW DOSE
Impact of Intranasal Corticosteroids on Childhood Growth

Don’t know much about combined intranasal and inhaled delivery in child with allergic rhinitis and asthma!

Summary of the ICS Growth Effect in Children

- Real, reproducible, small and dose- and device-dependent.
- Can be seen at low doses.
- Small variations in magnitude across the various ICS’s and individual children.
- Effect on final adult height unknown.
- FDA: This is a Class Effect. The potential growth effects of prolonged treatment with ICS should be weighed against clinical benefits obtained and the availability of safe and effective non-corticosteroid treatment alternatives.
- Use safest steroid available at lowest effective dose, and address “steroid phobia” proactively with parent to minimize effect on adherence.
- Risk is manageable and does not discourage use of ICS in appropriately selected children.

BALANCING SAFETY AND EFFICACY OF ICS


- Pick safe(est) drug
- Use lowest effective dose
- Optimize steroid-sparing strategies (environment, vaccines, concomitant disease, add-on* therapy)
- Consider first-line trial of ICS alternative (LTRA) in some of the mildest patients
- Consider add-on* to ICS (vs. doubling/tripling ICS dose) when control is inadequate, particularly for exercise control
- Consider add-on* therapy when ICS dose is high
- Monitor:
  - Growth in all children
  - Other SSEs at high doses (BDP ≥ 1,600 mcg/d in adult, ≥ 800 mcg/d in child)
Do Inhaled Corticosteroids Really Affect Growth?

- Yes
- Debatable whether or not effect is significant
- Debatable whether or not we actually see this in practice because such a small effect size is difficult to detect and because of low adherence rates

Is a 1 cm/year Reduction in Growth Velocity Significant?

“Statistically”: Yes

“Clinically”, It Depends:

Yes, if:
1) No systemic bioavailability is desired;
2) Child has a growth disorder;
3) Effect is cumulative and adult height is affected;
4) Parents believe height is linked to future success;
5) Parents want child to play in NBA.

No: For most children who just want to enjoy activity without asthma symptoms.

Which one might have used steroids?
TRANSIENT SHORT STATURE - ANY HARM?

Deborah Gentile, MD (Director)
Temple University
Giovanni Piedimonte, MD (Director & Founder)
West Virginia University
David P. Skoner, MD (Director & Founder)
Temple University and West Virginia University
Sally E. Wenzel, MD (Director)
University of Pittsburgh
Andrej Petrov, MD (Fellow Program Director)
University of Pittsburgh
Sergei Belenky, MD, PhD (Planning Committee)
University of Pittsburgh
Philip Fireman, MD (Planning Committee)
University of Pittsburgh

www.nemacolinasthma.org

Visit Our Websites