Asthma Therapy & Adrenal Suppression In Children

Alexandra Ahmet
Great Plains Endocrine Symposium 2016
Disclosure

CME
- Nycomed
- Takeda

Advisory Boards
- Nycomed
- Reveragen

Research
- Nycomed
Overview

- Physiology
- Oral steroids & suppression
- Testing
- Inhaled corticosteroids (ICS) & suppression
- Recommendations
ICS = Essential Asthma Therapy

- Eliminates or reduces chronic symptoms of asthma
- Prevents exacerbations
- Maximizes lung function
- Reduces need for rescue beta agonist
- Enables normal activity and exercise

- Reduces hospitalizations
  - Suissa et al. 2002

- Reduces asthma death rate
  - Ernst et al. 1992
Possible Side Effects

- Adrenal suppression
- Growth suppression
- Osteoporosis
- Obesity
- Cushingoid features
- Hypertension
- Hypercholesterolaemia
- Diabetes
- Increase infection risk

- Myopathy
- Cataracts
- Glaucoma
The Case

ID
- 5 ½ yo girl with asthma

HPI
- Unwell x 12 hours
- Unable to rouse in AM

ER
- Treated for hypoglycemic seizure

ICU x 2 months
- Encephalopathic
- w/u metabolic/infectious/neurological -ve
The Case

PMH
- Asthma
- Flovent > 500mcg/day

Chest Clinic
- malaise/fatigue/headache/poor growth
- r/o adrenal suppression
The Case - Growth
The Answer to the Case

ACTH stimulation test:
- Basal & peak cortisol levels <25 nmol/L
Why Does This Child Have Adrenal Suppression?

a) All children taking ICS are at moderate risk of adrenal suppression.

b) Children receiving $\geq 500$ mcg of fluticasone are at moderate to high risk of adrenal suppression.

c) Only children receiving $> 1000$ mcg of fluticasone are at risk of adrenal suppression.

d) She must have received PO steroids that her parents are not reporting.
HPA Axis Suppression & Steroids
The Circadian Rhythm

[Diagram showing plasma concentration of ACTH and cortisol over 24 hours with key times marked: 12:00 P.M., 6:00 P.M., 12:00 A.M., 6:00 A.M., 12:00 P.M.]

Plasma concentration

ACTH

Cortisol

Mean value

Transient fluctuations

Time of day

12:00 P.M. 6:00 P.M. 12:00 A.M. 6:00 A.M. 12:00 P.M.
Circadian Regulation

Hypothalamus

Stressors

Vasopressin &
Pro-inflammatory cytokines

CRH

Pituitary

ACTH

Adrenals

Cortisol

THE HPA AXIS
Adrenal Suppression

The HPA Axis

Glucocorticoids
Adrenal Insufficiency

Glucocorticoid
- Weakness/fatigue
- Malaise
- Nausea/vomitting
- Headache
- Poor weight gain
- Poor growth
- Myalgia/arthralgia
- Psychiatric symptoms
  - Hypoglycemia
  - Hypotension

Mineralocorticoid
- Salt craving
- Weight loss
- Volume depletion
- Hypotension
- Hyponatremia
- Hyperkalemia
Oral Steroids and Suppression

- Dose
- Duration
- Timing
- Frequency
- Time for recovery (days-years)

Stress and Adrenal Insufficiency

- Several reported cases of hypotension/death during surgery
- Decreased ability to fight infection
- Need for STRESS COVERAGE

Shulman, J Pediatrics, 2007
Axelrod, Endocrinol Metab Clin N 2003
Rix, J Peds, 2005
Testing
How do we test for Adrenal Suppression?

Gold Standard:
- Insulin induced hypoglycemia test

Best Test:
- Low Dose (1 mcg) ACTH stimulation test
- ? Peak cortisol >500 nmol/L

Considerations:
- Morning test
- Reduce or eliminate tubing
- Peak 20-30 minutes
- HOLD glucocorticoids x 24 hours

How do we test for Adrenal Suppression?

First morning cortisol:
- **8 AM** cortisol
- < 50-100 nmol/L – rule in A.S.
- >350-500 nmol/L – rule out A.S.
- >275 nmol/L ? screening threshold in asymptomatic

Considerations:
- Pubertal status
- HOLD glucocorticoids

Testing Challenges

- Differences between immunoassays
- Measurement of total (not free) cortisol
- Significance of “borderline” stimulated results

Future considerations

- Mass spectrometry
- Measurement of free cortisol / Cortisol binding globulin
- Further study of clinical significance of borderline results

Kazlauskaitė, Endocr Dev, 2010; Grusen, Endo Abstr 2012
The case – The aftermath

- Fluticasone gradually weaned
- Gradual normalization of ACTH stim test
- Stress steroids for infection
- 8 months (off steroids x 2mo)
  - cortisol peak >500nmol/L
  - energy much improved
  - asthma well controlled on steroid sparing agents
The Case - Growth Post d/c of ICS
Inhaled Corticosteroids & HPA Axis Suppression
Evidence: Acute Adrenal Crisis (AAC) Associated with ICS

2912 questionnaires (pediatricians and endocrinologists)

33 patients (500 – 2000 mcg/day ICS) Met diagnostic criteria for AAC associated with ICS

23 Children had acute hypoglycemia
5 children had insidious onset of symptoms

4 Adults had insidious onset of symptoms
1 adult had hypoglycemia and convulsions
Symptomatic AS among children in Canada

Two year surveillance study Canadian Paediatric Surveillance Program (CPSP)
- 46 cases symptomatic AS, 6 cases adrenal crisis
- Growth failure and/or non-specific symptoms
- **37 children (80%) received ICS** (alone or with other GC)

Conclusions:
- Although rare, significant AS can lead to significant morbidity
- Children being treated for Asthma are at risk
- Children with poor growth or non-specific symptoms should be tested for AS
The Fate of Inhaled Corticosteroids

- **Mouth and pharynx**: 10 - 50% Deposited in lung
- **GI tract**: 60 - 90% Swallowed (reduced by spacer or mouth rinsing)
- **Lung**: Complete absorption from the lung
- **Systemic Circulation**: Systemic side effects
- **Liver**: Orally bioavailable fraction, First-pass inactivation
- **Orally bioavailable fraction**: A.S.

Barnes, 2007
Factors that Affect Systemic Bioavailability and Bioactivity of ICS

- Dose
- Formulation & Delivery System
- Physiological Factors
- Buccal Absorption
- Intestinal Absorption
- Lung Absorption
- Post absorption Pharmacokinetics
- Pharmacodynamics

Systemic Bioavailability


Slide created by Ric M Procyshyn
Biochemical evidence of HPA axis suppression on ICS

≥ 500 mcg/day fluticasone high risk inter-individual susceptibility

- Smith, Ped and Child Health, 2012
- Lipworth, Arch Intern Med, 1999
- Mahacholklertwattana, Arch Dis Child, 2004
- Paton, Arch Dis Child, 2006

Adrenal suppression rare on low dose ICS therapy

- Smith, Ped and Child Health, 2012
- Bacharier, Pediatrics, 2000;
- Pescollderungg, Thorax, 2003
## Recommendations - Screening Thresholds AS (Daily ICS dose, mcg)

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Trade Name</th>
<th>Threshold (6-11 years)</th>
<th>Threshold (12 and older)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate (HFA)</td>
<td>QVAR</td>
<td>≥400</td>
<td>≥400</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Pulmicort</td>
<td>≥800</td>
<td>≥800</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>Alvesco</td>
<td>&gt;400</td>
<td>&gt;400</td>
</tr>
<tr>
<td><strong>Fluticasone propionate</strong></td>
<td>Flovent</td>
<td>≥500</td>
<td>≥500</td>
</tr>
<tr>
<td>Fluticasone furoate</td>
<td>Arnuity* Ellipta</td>
<td>≥100</td>
<td>≥100</td>
</tr>
<tr>
<td>Mometasone</td>
<td>Asmanex Twisthaler</td>
<td>N/A</td>
<td>≥800</td>
</tr>
</tbody>
</table>

Ahmet et al. CPS statement, DRAFT 2016

Breakdown of Common ICS Doses:
Total average daily dose for ages 0-11 (all indications)

Fluticasone

- 500 mcg* 42.8%
- 200 mcg
- 250 mcg
- 100 mcg
- Other

IMS Health Canada, Jan – March 2010.
Clinical evidence of HPA axis suppression on ICS

- Several reports of adrenal crises
- Hypoglycemic symptoms
- Suppressed ACTH stimulation tests
- Most: fluticasone ≥500-mcg/day

Dunlop, Pediatr Pulmonol, 2002
Patel, Arch Dis Child, 2001
Randell, Pediatr Drugs, 2003
Allen, Metabolic Clinics NA, 2005
Todd, Arch Dis Child 2002
## Corticosteroid exposure prior to presentation with adrenal suppression

<table>
<thead>
<tr>
<th>Case</th>
<th>Inhaled corticosteroids</th>
<th>Oral corticosteroids</th>
<th>Other Meds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Type</strong></td>
<td><strong>Dose</strong></td>
<td><strong>Duration</strong></td>
</tr>
<tr>
<td>1</td>
<td>Fluticasone</td>
<td>125-250 ug BID</td>
<td>11 months</td>
</tr>
<tr>
<td>2</td>
<td>Fluticasone</td>
<td>125-250ug BID</td>
<td>6 years</td>
</tr>
<tr>
<td>3</td>
<td>Fluticasone</td>
<td>250 ug BID</td>
<td>3 years</td>
</tr>
<tr>
<td>4</td>
<td>Fluticasone</td>
<td>250 ug BID</td>
<td>4 years</td>
</tr>
</tbody>
</table>

*CS = corticosteroids

Adapted from M.Kupfert Heller, J Lacks, T Kovesi and A Ahmet, Asthma, 2010
## Symptoms of AS and adrenal function before & after adrenal recovery

<table>
<thead>
<tr>
<th>Case</th>
<th>Presenting Symptoms</th>
<th>AM Cortisol Pre-CIC Normal ≥171</th>
<th>AM (Normal &gt;171)</th>
<th>Stimulated (Normal&gt;500)</th>
<th>Time to recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cortisol screen</td>
<td>56</td>
<td>255</td>
<td>587</td>
<td>5 months</td>
</tr>
<tr>
<td>2</td>
<td>Hypoglycaemic seizure</td>
<td>9</td>
<td>174</td>
<td>490</td>
<td>4 months</td>
</tr>
<tr>
<td>3</td>
<td>Cortisol screen</td>
<td>82</td>
<td>204</td>
<td>579</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>Decreased energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cortisol screen</td>
<td>50</td>
<td>195</td>
<td>566</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>Decreased energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

Adapted from M.Kupfert Heller, J Lacks, T Kovesi and A Ahmet, Asthma, 2010
Possible risk factors for AS

Possible Risk Factors

- Higher ICS dose
- Concomitant nasal corticosteroid use
- Concomitant use of CYP3A4 inhibitors
- Cumulative glucocorticoid dose

Associations

- Low BMI
- Poor growth
- Cushingoid features

Goldbloom, CPSP, 2016; Ahmet, AACI, 2011; Kapadia, JAMA, 2016; Zollner, Pediatrics, 2012
Growth & HPA suppression with ICS

- Poor growth is a common association with AS

- However, height SDS change NOT a sensitive predictor of adrenal suppression

- Growth and adrenal suppression can be independent of ICS

Goldbloom and Ahmet, Archives of Disease and Child in press 2016; Dunlop, Arch Dis Child, 2004
Who should be tested?

- Symptomatic AS
- Growth failure, weight loss, anorexia
- High dose ICS
- Long term IN or periodic PO GC
- Low BMI = additional R.F
PES Drugs and Therapeutics Committee Recommendations 2016

Symptomatic
- a.m. cortisol <3ug/dL (83nmol/L) = A.S.
- a.m. cortisol >3ug/dL → LDST
- LDST <18ug/dL (495nmol/L) = A.S.

Asymptomatic
- a.m. cortisol <3ug/dL = likely A.S. → LDST
- a.m. cortisol >10ug/dL (275nmol/L)=unlikely A.S.
- a.m. cortisol 3-10ug/dL → refer to specialist

* All cases of proven A.S. should be managed by a specialist

Kapadia, JAMA, 2016
Recommendations
CPS/CPEG
Position Statement DRAFT
Recommendations
All Patients

- Lowest possible dose ICS
  - Regular re-evaluation
- Physician and patient/family awareness of potential for AS
- Education that ICS benefit > risk & that compliance and appropriate f/u = best prevention
- Empiric stress dosing for critical illness or surgery during and x 1-2 years post ICS (draw cortisol prior to treatment)
- Physician awareness of the limitations of cortisol testing
Recommendations
Who should be screened?

- High (and high moderate) dose ICS (table) for >3 months
- Systemic GC for >2 weeks or >3 cumulative weeks in 6 months
- Concomitant CYP3A4 inhibitors
- Poor linear growth
- Cushings features
- Symptoms of AS
- Consider if more than one form of GC
- Planned surgery
### Recommendations - Screening Thresholds AS  
(Daily ICS dose, mcg)

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Ahmet et al. DRAFT 2016

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Recommendations
Who should be screened?

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- Concomitant CYP3A4 inhibitors
- Poor linear growth
- Cushings features
- Symptoms of AS
- Consider if more than one form of GC
- Planned surgery
Recommendations - How to screen?  
First morning cortisol

**Procedure**
- 8 a.m. test
- Hold PO GC the evening before and morning of the test
- Hold ICS the evening before and morning of the test
- Consider fasting

**Results**
- a.m. cortisol <100 nmol/L = likely A.S.
- a.m. cortisol 100-275 nmol/L = possible A.S.
- a.m. cortisol >275 nmol/L = A.S. unlikely if *asymptomatic*
Recommendations - Screening and Management of Asymptomatic Patients

A.M. cortisol < 100nmol/L = likely A.S.

- Daily physiologic & Stress dosing GC
- Patient education
- Stress dosing card
- Endocrine consult
Recommendations - Screening and Management of Asymptomatic Patients

A.M. cortisol 100-275nmol/L = possible A.S.

- Refer to endocrinology if <2 years of age
- Empiric stress dosing for mild to severe stress
- Stress dosing card
- Repeat cortisol q 3-6 months
- Consider LDST or referral to endo if remote travel/housing
- LDST 1 year post ICS d/c if a.m. cortisol <275 nmol/L
- Refer to endocrinology abnormal LDST (peak <500 nmol/L)
Recommendations - Screening and Management of Asymptomatic Patients

A.M. cortisol >275 nmol/L = clinically significant A.S. unlikely

- Repeat a.m. cortisol every 3-6 months
- Empiric stress dose for critical illness or surgery
Recommendations - Screening and Management of Symptomatic Patients

Adrenal crisis
- Draw cortisol and treat

Symptomatic A.S. → low dose ACTH stim test
- Peak<500nmol/L = A.S.
- Initiate physiological daily and stress dosing GC
- Consult endocrinology
- Peak >500nmol/L = AS very unlikely
- Investigate for other etiology of symptoms

Ahmet et al. DRAFT 2016
# Recommendations
## Treatment of A.S.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Hydrocortisone dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal crisis, severe illness or injury</td>
<td>100mg/m2 IV/IM (max 100mg) stat then 100 mg/m2/day over 24 hours (max 200mg)</td>
</tr>
<tr>
<td>Surgery</td>
<td>50-100mg/m2 pre-op then 100 mg/m2/24 hours IV (max 100mg) over 24 hours</td>
</tr>
<tr>
<td>Mild to moderate illness</td>
<td>30mg/m2/day divided TID Reassess if duration &gt;3 days</td>
</tr>
<tr>
<td>Vomiting / unable to tolerate PO</td>
<td>Must be given parenterally 25mg hydrocortisone q 6 hourly IV or q 8 hourly IM</td>
</tr>
<tr>
<td>Daily physiologic dosing</td>
<td>8 mg/m2/day</td>
</tr>
<tr>
<td>Remote travel / housing</td>
<td>Teaching IM solucortef</td>
</tr>
</tbody>
</table>

Ahmet et al. DRAFT 2016
Adrenal Suppression with ICS
Take Home Messages

- Adrenal crisis occurs

- \(\uparrow\) dose ICS in most clinically significant A.S.

- Education and responsible prescribing of ICS is essential

- Poor growth or possible symptoms of A.S. \(\rightarrow\) Test

- \(\uparrow\) dose ICS or other risk factors \(\rightarrow\) screen

- A.S. can persist after discontinuation of GC
Thank you!

Questions?
## Pharmacological Characteristics of ICS

<table>
<thead>
<tr>
<th></th>
<th>Fluticasone HFA</th>
<th>Budesonide DPI</th>
<th>Beclomethasone HFA</th>
<th>Ciclesonide HFA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protein binding</strong></td>
<td>90-91%</td>
<td>85-90%</td>
<td>87%</td>
<td>98-99%</td>
</tr>
<tr>
<td><strong>Lung deposition</strong></td>
<td>12-20%</td>
<td>22-42%</td>
<td>50-60%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>Oral bioavailability</strong></td>
<td>&lt;1%</td>
<td>11%</td>
<td>15%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Particle size</strong></td>
<td>2.8μm</td>
<td>&gt;2.5μm</td>
<td>&lt;2.0μm</td>
<td>&lt;2.0μm</td>
</tr>
<tr>
<td><strong>Clearance Rate (L/h)</strong></td>
<td>66</td>
<td>84</td>
<td>150/120</td>
<td>152/228</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Twice/day</td>
<td>Twice/day</td>
<td>Twice/day</td>
<td>Once/day</td>
</tr>
<tr>
<td><strong>Adrenal Suppression</strong></td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>- (to date)</td>
</tr>
</tbody>
</table>

Adapted from Ahmet et al, AACI, 2011
# Glucocorticoids: Common Features

<table>
<thead>
<tr>
<th></th>
<th>Duration of Action</th>
<th>Anti-inflam Potency</th>
<th>HPA Suppr Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (hydrocort)</td>
<td>Short</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone/ Prednisolone</td>
<td>Short</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Methylpred</td>
<td>Short</td>
<td>5</td>
<td>5*</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Long</td>
<td>30</td>
<td>70-80</td>
</tr>
</tbody>
</table>

Hansen JW, Pediatrics, 1976
Rivkees, Pediatrics, 2000
Up to Date, 2007
Factors that Affect Systemic Bioactivity of ICS

- Systemic bioactivity (e.g., adrenal suppression) of ICS is dependent on the following:
  - Overall systemic bioavailability of ICS
    - Buccal, intestinal and lung absorption
  - Post absorption pharmacokinetics
    - Metabolism/biotransformation of the active compound
    - Protein binding
    - Half-life
    - Systemic Clearance
  - Pharmacodynamics
    - Interaction between the ICS and the glucocorticoid receptor

### PK and PD factors that contribute to risk of systemic side effects of ICS

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing</strong></td>
<td>Increase in dosing frequency may result in reduced compliance</td>
<td>Increase in dosing frequency increases the potential for local and systemic side effects</td>
</tr>
<tr>
<td><strong>Lung deposition</strong></td>
<td>Greater lung deposition (lung bioavailability) increases efficacy</td>
<td>Greater lung deposition (lung bioavailability) increases systemic bioavailability and thereby increases the potential for systemic side effects</td>
</tr>
<tr>
<td><strong>Glucocorticoid receptor affinity</strong></td>
<td>High receptor-binding affinity correlates positively with increased efficacy</td>
<td>High receptor-binding affinity increases the potential for both local and systemic side effects</td>
</tr>
</tbody>
</table>

*Slide created by Ric M Procyshyn Pharm*

Derendorf et al., Eur Respir J 2006; Kelly, HW. Ann Pharmacother 2009
Bioavailability

| PK and PD factors that contribute to risk of systemic side effects of ICS |
|-------------------|----------------------------------|
| **Efficacy** | **Safety** |
| High pulmonary bioavailability is necessary for efficacy | Increased systemic bioavailability increases the potential for systemic side effects. Systemic bioavailability is a function of the sum of pulmonary and oral bioavailability |
| Not applicable as this parameter pertains to the systemic circulation and not lung tissue | High plasma protein binding reduces the potential for systemic side effects since only the free drug is pharmacologically active |

*Slide created by Ric M Procyszyn*
*Derendorf et al., Eur Respir J 2006;Kelly, HW. Ann Pharmcother 2009*
PK and PD factors that contribute to risk of systemic side effects of ICS

<table>
<thead>
<tr>
<th></th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>Not applicable as half-life refers to systemic circulation and not lung tissue. Pulmonary retention time is more relevant in this case</td>
<td>The longer the half-life the greater the potential for systemic side effects</td>
</tr>
<tr>
<td>Clearance</td>
<td>Not applicable as this parameter pertains to the systemic circulation and not lung tissue</td>
<td>The greater the clearance the less potential for systemic side effects</td>
</tr>
</tbody>
</table>

*Slide created by Ric M Procyshyn
Derendorf et al., Eur Respir J 2006; Kelly, HW. Ann Pharmcother 2009*