Objectives

- To review HPA axis suppression and its clinical significance in adults and children
- To describe methods for diagnosing HPA axis suppression
- To explain the implication on selection of treatment for asthma and allergic diseases
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The HPA Axis

- Pituitary gland
- Hypothalamus
- CRH
- ACTH
- Adrenal glands
- Cortisol
Exogenous Prednisone 7.5mg or Dexamethasone 0.75mg for 3+ Weeks........

- Decreased CRH
- Decreased ACTH
- Decreased cortisol (0800 concentration)
- Decreased response to stimulation with cosyntropin 1 mcg (low dose stimulation)
Implications of HPA Suppression

- No clinical adverse effects and asymptomatic
- Subnormal secretion of Cortisol (at baseline or with stimulation) and asymptomatic....or
- Suppression of growth
- Osteopenia
- Severe Myalgia, Weakness, Fatigue
- Inability to respond to stress (surgery, shock, sepsis etc)
- Cushingoid obesity/syndrome
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Methods for Diagnosis

- Testing the Hypothalamus
- Testing the Pituitary
- Testing the Adrenals
- Testing the whole axis
Testing Adrenal Function

- Insulin Tolerance Test (whole axis)- unpleasant (need glucose <40mg/dL); risky if cardiovascular disease, elderly, seizure disorders
- ACTH- Cosyntropin.....(can miss secondary adrenal insufficiency with 250 mcg)
- Metyrapone (not available in U.S.) test-risk of temporary adrenal insufficiency
- Corticotropin-Releasing Hormone (CRH) has lower sensitivity (76%) but high specificity (96%)
Relevant to Asthma...

Adrenal Insufficiency

Primary
(Addisons Disease--Autoimmune, TB)

Secondary
(Corticosteroids)
Diagnosis of Secondary Adrenal Insufficiency from Corticosteroids

- **Background:** Oral or high dose orally inhaled corticosteroids block release of CRH and ACTH
- Low cortisol
- Impaired response to ACTH (Cosyntropin) low dose-1 mcg vs higher dose-250 mcg)
- Impaired or no response to CRH
Exogenous Prednisone 7.5mg or Dexamethasone 0.75mg for 3+ Weeks

- Decreased CRH
- Decreased ACTH
- Decreased 0800 cortisol

Is there low basal cortisol (<5 mcg/dL or if 5-13 mcg/dL, then needs stimulation test)?

Is there a normal stimulated response of cortisol mcg/dL? (LST > 22 mcg/dL, HST > 30 mcg/dL)

If subnormal response to stimulation, need insulin tolerance test or metyrapone test
Primary Study Outcomes—is there blunted or reduced

- **Basal** HPA Axis-Serum Cortisol AUC $0-24 \text{ hr}$
- **Dynamic** HPA Axis-response to low dose cosyntropin
- **Clinically meaningful suppression** is when cosyntropin response is impaired...in patients with asthma
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Mean (± SE) percent change in serum cortisol AUC0–24h following 29 days of treatment with PBO, CIC 640, CIC 1280, FP 880, and FP 1760.


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Mean (± SE) change from baseline in serum cortisol AUC0–24h over time for PBO, CIC 640, CIC 1280, FP 880, and FP 1760.

Prestimulation and peak serum cortisol values following the administration of 1 µg of cosyntropin at baseline (top) and at 30 days end of study (middle).


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Systemic Absorption of Inhaled Corticosteroid Dry Power Inhalers in Patients Matters

- Less in patients with asthma compared to normal subjects
- Drug specific
Mean (SE) plasma concentrations of (A) fluticasone propionate and (B) budesonide in healthy subjects and subjects with moderately severe asthma.

Harrison T W, Tattersfield A E Thorax 2003;58:258-260

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Plasma Cortisol AUC 2000 to 0800
Plasma Cortisol AUC 2000 to 0800
Is There Additive HPA Suppression When There Is Nasal and Bronchial Administration?

- Yes or No?
- Which route results in more systemic absorption?
PATIENTS ≥ 12 YEARS

FLUTICASONE PROPIONATE (FP)

ORALLY INHALED FP 88 OR 220 MCG BID BY METERED DOSE INHALER...26 WEEKS

FP 250 MCG OR FP/SALMETEROL 250/50 BY DISKUS (DRY POWDER)...12 WEEKS

NASAL FP

AM CORTISOL AND POST-STIMULATION
METHODS TO DETECT ABNORMAL RESPONSES

- BASAL CORTISOL 0800.. ? WERE < 5 MCG/DL

- POST STIMULATION PEAK CORTISOL...
  < 18 MCG/DL

- POST STIMULATION RISE OF < 7 MCG/DL
Is There Additive HPA Suppression When There Is Nasal and Bronchial Administration?

- Yes or No? NO

- TRIVIA QUESTION: Which route results in more SYSTEMIC absorption? NASAL
SUMMARY

- COMBINATIONS OF INTRANASAL AND ORALLY INHALED CORTICOSTEROIDS IN RECOMMENDED DOSES WOULD NOT CAUSE HPA AXIS ABNORMALITIES

- FIRST PASS EFFECT (LIVER METABOLISM) MINIMIZES ORAL BIOAVAILABILITY (FLUTICASONE, MOMETASONE, BUDESONIDE, CICLESONIDE < BECLOMETHASONE DIPROPIONATE)