Glucocorticoid therapy and stress dosing in CAH

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Hormones in the adrenal glands

- Adrenal cortex
  - Outer layer: aldosterone
  - Middle layer: cortisol
  - Inner layer: androgens or male hormones

- Adrenal medulla
  - Catecholamines – epinephrine and norepinephrine
Hypothalamic-Pituitary-Adrenal Axis

- Hypothalamus
- Corticotropin releasing hormone (CRH)
  - +
- Pituitary
  - + Adrenocorticotropic hormone (ACTH)
- Adrenal glands
  - Androgens
  - -
- Cortisol
Adrenal steroid pathway

Medications in CAH

• Aldosterone replacement
  – Fludrocortisone
  – Salt in infancy

• Cortisol replacement
  – Glucocorticoids
    • Hydrocortisone
    • Prednisone
    • Dexamethasone

“Cortisol dependent” or “Adrenal insufficiency”
Dosing of medications

- **Fludrocortisone**: based on plasma renin activity level, electrolytes, and blood pressure
  - e.g. 0.05 to 0.20 mg/day

- **Salt**: based on weight and electrolytes
  - e.g. 1-2 grams/day (17-34 mEq/day) in infancy

- **Glucocorticoids**: based on calculated body surface area (BSA) and adrenal androgen levels
  - e.g. 10-20 mg/m²/day
Various glucocorticoids are available

- **Hydrocortisone** – tablets or suspension?
  - Can crush and dissolve in water
  - Needs to be given three times a day

- **Prednisone or Prednisolone** – tablets or liquid
  - 5 to 10 x (or more) stronger than hydrocortisone
  - Needs to be given twice a day

- **Dexamethasone** – tablets or liquid
  - 25 to 100 x (or more) stronger than hydrocortisone
  - Given only once a day – very potent and long-acting
Hydrocortisone delivery using a pump

- Compared continuous subcutaneous hydrocortisone infusion (CSHI) to conventional oral glucocorticoid therapy
- 8 adult patients with poorly controlled CAH
- Pump was able to:
  - Approximate physiologic cortisol secretion
  - Improved adrenal steroid control
  - Positive effects on quality of life
  - Safe and well tolerated

Other experimental options

- **Modified release formulations**
  - Chronocort®
  - Plenadren®

- **Multi-drug regimen at the NIH**
  - Anti-androgen
  - Aromatase inhibitor
  - Lower dose of glucocorticoid

Mallappa A et al. *J Clin Endocrinol Metab*, 2015
Why is there so much variability in glucocorticoid dosing?

Why is there so much variability in glucocorticoid dosing?

- Compliance?
- Different degrees of endogenous enzyme activity?
- Other genetic factors?
  - *ABCB1* (or *MDR1*)
  - *NR3C1*
  - *IPO13*
Single nucleotide polymorphisms
Genetic variants in the gene \textit{ABCB1}
Stress steroids – oral

• Very important – this can be life-saving!

• Triple oral glucocorticoid if have a fever, illness, or stress

• Continue to give stress oral steroids for an additional 24 hours after back to baseline and feeling well
Stress steroids – injection

- If vomiting and unable to keep down stress oral steroids, then need to give injectable hydrocortisone
  - 100 mg, 250 mg, 500 mg, or 1000 mg
  - 50-100 mg/m² IM x1
  - Then the child should be evaluated by a doctor and go to the Emergency Room
Stress steroids – in the hospital

- Hydrocortisone 50-100 mg/m^2 IV x1, then...

- Hydrocortisone 50-100 mg/m^2/day IV divided every 6 hours
  - Do not need fludrocortisone and salt when on IV stress doses of hydrocortisone

- As patient starts to drink and eat, can switch to triple oral dosing
CAH compromises both the development and function of the adrenal medulla.

**Controls**
- Normal appearance of adrenal cortex and medulla
- Normal stores in medulla of epinephrine and norepinephrine

**CAH**
- Poorly defined zones of cortex and incomplete formation of medulla
- Depleted stores in medulla

Patients with CAH have decreased epinephrine reserve in adrenal medulla

Short term high-intensity exercise

Prolonged moderate-intensity exercise

Epinephrine deficiency – what does this mean???

- No evidence that additional hydrocortisone given before exercise or physical activity is beneficial.

- Epinephrine deficiency may be responsible for increased susceptibility to develop hypoglycemia in children with CAH during an illness – also at risk for delayed recognition and treatment.

- Carbohydrate and glucose supplementation during illness with fever is very important in children with CAH.
Consequences of over treatment

- Poor linear growth → short stature
- Weight gain → obesity
- Striae
- Elevated blood pressure
- Reduced bone density
Blood pressure and CAH

• A clear consensus on the incidence of hypertension in individuals with CAH does not exist – additional research is needed

• Potential reasons for hypertension:
  – Obesity
  – Too high of a dose of fludrocortisone
  – Too high of a dose of glucocorticoid
  – Is there something else going on?
Experience at Riley Hospital

• The incidence of hypertension (6.6%) in our patients with CAH is higher than what is expected in the general pediatric population
  – 1% prevalence in all children
  – 4.5% prevalence in overweight children

• Dose of fludrocortisone and glucocorticoid were not different between groups and not excessive

• Obesity was not a determining factor in the development of hypertension

Nebesio TD, Eugster EA. *Endocrine, 2006*
Consequences of under treatment

• Sodium and potassium imbalance

• Excess androgen production
  – Increased linear growth but ultimately leads to early growth plate closure and short stature as an adult
  – Pubic hair and acne
  – Fertility problems
Summary

• The care of children with CAH is complex
• Steroid dosing needs to be individualized
• Compliance with medications is important in regards to growth and overall health – importance of stress dosing
• Always remember to wear some type of medical alert ID!