Practical Management of Steroids in Non-Endocrine Practice

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Outline

• Epidemiology of steroids

• Case Presentation 1
  o General management of steroids
  o Glucocorticoid induced osteoporosis
  o Glucocorticoid induced hyperglycaemia

• Case Presentation 2
  o Glucocorticoid induced adrenal suppression
  o Adrenal crisis and sick day rules
Epidemiology of Steroid Use

N = 244, 235

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory System</td>
<td>39.9%</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>6.2%</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td>6.2%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>3.4%</td>
</tr>
<tr>
<td>Digestive system</td>
<td>2.8%</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>2.3%</td>
</tr>
<tr>
<td>Circulatory system</td>
<td>1.9%</td>
</tr>
<tr>
<td>Injury &amp; poisoning</td>
<td>1.3%</td>
</tr>
<tr>
<td>Unknown</td>
<td>20.4%</td>
</tr>
</tbody>
</table>

Van Staa TP et al, Q J Med 2000; 93:105-111
## Properties and dose equivalents to HC

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Approx equivalent dose (mg)</th>
<th>Relative glucocorticoid effect</th>
<th>Relative mineralocorticoid effect</th>
<th>Duration of effect (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>8 – 12</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25</td>
<td>0.8</td>
<td>0.8</td>
<td>8 – 12</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>4</td>
<td>0.8</td>
<td>12 – 36</td>
</tr>
<tr>
<td>Methyl prednisolone</td>
<td>4</td>
<td>5</td>
<td>Minimal</td>
<td>12 – 36</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>30</td>
<td>Minimal</td>
<td>36 – 72</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.6</td>
<td>30</td>
<td>Negligible</td>
<td>36 – 72</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>0.05 – 0.1</td>
<td>10-15</td>
<td>125 - 150</td>
<td>12 – 36</td>
</tr>
</tbody>
</table>
Adverse effects related to cumulative dose

\[ N = 2167 – SE \text{ were common affecting at least 90\% of subjects} \]

Q1: <1.7g  
Q2: 1.7 – 2.8g  
Q3: 2.9 – 4.7g  
Q4: >4.7g  

* Also related to low dose <7.5mg/day prednisolone

Curtis et al Arthritis and Rheumatism 2006 55: 420 - 426
# Adverse effects related to daily dose

<table>
<thead>
<tr>
<th>Linear effect (&lt;5mg to &gt;7.5mg)</th>
<th>Threshold effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cushingoid phenotype</strong>&lt;br&gt;Ecchymosis&lt;br&gt;Leg oedema&lt;br&gt;Thin skin&lt;br&gt;Sleep disturbances&lt;br&gt;Fractures</td>
<td><strong>Low Dose (~ &lt;5 – 7.5mg/day Pred)</strong></td>
</tr>
<tr>
<td><strong>Eye cataract</strong>&lt;br&gt;Adrenal suppression</td>
<td><strong>High dose (~ &gt;5 – 7.5mg/day Pred)</strong></td>
</tr>
<tr>
<td>Epistaxis&lt;br&gt;Weight gain&lt;br&gt;Low BMD&lt;br&gt;Infections&lt;br&gt;High blood glucose&lt;br&gt;Depression&lt;br&gt;Glaucome</td>
<td><strong>Increased blood pressure</strong>&lt;br&gt;CV events&lt;br&gt;Myopathy&lt;br&gt;Psychiatric disturbances&lt;br&gt;Mortality</td>
</tr>
</tbody>
</table>
Case Presentation 1

• Dear Physician,

I would be really grateful if you could see this patient who has been diagnosed with polymyalgia rheumatica and who is to start long term steroids. Your advice how to manage her steroids will be appreciated. She is concerned about side effects.

Thanks for your help
Monitoring patients on steroids

Baseline – Before starting or on first assessment
• History including total dose, date of initiation
• Weight, height, BMI, blood pressure
• FBC, Fasting blood glucose/Hba1c ± OGTT, Lipid profile, BMD

Continuation – Follow – up
• Annual height, enquire for fracture, BMD 1 year post GC initiation then every 2 to 3 years, assess for joint pain
• Consider lateral spine X-ray in adults >65 years and FRAX
• Assess CV risk, measure lipids, BP every 6 to 12 months
• Screen for diabetes during first 48 hours, every 3 to 6 months, then annually
• Annual ophthalmic assessment for cataracts and glaucoma
General advice to patients on steroids

• Prescribe the lowest effective dose for the shortest period of time

• Treat pre-existing co-morbid conditions and use GC sparing agents

• Sick day rules, steroid card

• Lifestyle recommendations – exercise, healthy diet, no smoking

• Avoid contact with infectious people and warn about pregnancy risks

• DO NOT STOP steroids abruptly
Drug interactions

• Drugs that impair metabolism by inhibition of Cytochrome P450 3A4
  o Anti-fungals
  o Antibiotics e.g. macrolides
  o Antivirals e.g. indinavir, ritonavir
  o Fluoxetine, diltiazem, cimetidine

• Drugs that accelerate metabolism by induction of Cytochrome P450 3A4
  o Anticonvulsants e.g. carbamazepine, phenytoin, phenobarbital
  o Rifampicin, Pioglitazone

• Drugs that increase CBG and may falsely elevate cortisol results
  o Oestrogens, mitotane
Fracture Risk Depends on the Dose of Glucocorticoids

Relative risk of fracture

Adapted from Van Staa TP et al, J Bone Miner Res 2000;15(6) 993-1000
Guidelines for GC-induced osteoporosis

- Commitment or exposure to oral glucocorticoids for ≥3 months

  - Age <65 years
    - No previous fragility fracture
      - Measure BMD (DXA scan, hip ± spine)
        - T score above 0
          - Reassure
          - General measures
        - T score between 0 and −1.5
          - General measures
        - T score −1.5 or lower
          - Repeat BMD in 1–3 yr if glucocorticoids continued

  - Previous fragility fracture or incident fracture during glucocorticoid therapy

  - Age ≥65 years
    - Investigations
      - General measures
        - Advise treatment:
          - Alendronate (L)
          - Alfacalcidol
          - Calcitonin
          - Calcitriol
          - Clodronate
          - Cyclic etidronate (L)
          - HRT
          - Pamidronate
          - Risedronate (L)
Glucocorticoid-induced hyperglycaemia

- **Group 1**: Non-diabetic subjects, no prednisolone
- **Group 2**: Non-diabetic subjects receiving prednisolone
- **Group 3**: Diabetic subjects receiving prednisolone

N=13
N=40
N=7

Burt et al JCEM 2011; 96: 1789 - 1796
Management of glucocorticoid induced hyperglycaemia - once daily dosing

Monitor BG in patients on steroids

If BG >12mmol/l on two occasions pre or post meals, to start gliclazide 40mg/day (to a maximum of 240mg)

If BG still >12mmol/l pre or post meals, consider 10 units basal human insulin preferably (NPH, Humulin I) or if persistent hyperglycaemia throughout day use basal insulin analogue

Adjust doses by 10 to 20% on a daily basis; adjust dose when steroid doses decreasing

Adopted from JBDS Management of Hyperglycaemia and Steroid Therapy
Management of glucocorticoid induced hyperglycaemia - multiple daily dosing

Monitor BG in patients on steroids

If BG >12mmol/l on two occasions pre or post meals, to start gliclazide 40mg bd (max 160mg bd)

If BG still >12mmol/l pre or post meals, consider basal, twice daily premixed or basal-bolus

Adjust doses by 10 to 20% on a daily basis; adjust dose when steroid doses decreasing

Adopted from JBDS Management of Hyperglycaemia and Steroid Therapy
Case Presentation 2

Dear Endocrinologist,

I would be grateful if you could see and advise about the possibility of getting this patient off steroids. She is 45y with difficult asthma but has been exacerbation free for the last 24 months, and is only on steroids. Her BMD shows osteopaenia and is keen to see if she can be free of steroids.

Best wishes,

Etc.
Case Presentation 2

- 45y
- Asthma since 16y
- On oral prednisolone for last 15 years
- Never on less than prednisolone 5mg
- Very keen to come off oral prednisolone
- Examination – mild Cushing’s
Case Presentation 2

• What is the likelihood that she has endogenous cortisol production?

• Assuming the asthma does not flare what are the chances of getting her off steroids?

• At what rate should the steroids be reduced?
Suppression of HPA axis

Exogenous glucocorticoids suppress HPA axis
Cortisol Circadian Rhythm

Acrophase: 0832h
(0759h - 0905h)

Nadir: 0018h
(2339h – 0058h)

MESOR: 143.6 nmol/L
(130.1-156.1)

Debono et al., JCEM 2009 94: 1548-1554
Steroid withdrawal protocol following long-term glucocorticoids

• Discuss with patient about goals
• Convert to prednisolone 5 to 7.5mg OD
• Reduce by 1mg every 1-2 months
• Monitor symptoms
• Monitor HPA status at prednisolone 3mg/day

• If inflammatory disease worsens and/or has another flare up - may be better to accept long-term glucocorticoids
• Consider alternate day dosing
Case 2 - Recovery of HPA axis

- **Cortisol (nM)**
- **ACTH (pg/ml)**

- Prednisolone: 4mg, 3mg, 2mg, 1mg

- 'Pass' on synacthen test

- ACTH Normal range

- 30 minute cortisol

- Basal cortisol

Also see “Graber et al JCEM 1965; 25: 11 – 16”
Assay cross reactivity

Cross reactivity of exogenous glucocorticoid with serum cortisol immunoassay

- Hydrocortisone: 100%
- Cortisone acetate: up to 100%
- Prednisolone: up to 30%
- Prednisone: up to 30%
- Dexamethasone: zero
Does this patient on steroids have tertiary adrenal insufficiency?

Confirm patient on treatment glucocorticoids and record history

When on pred dose equiv ≤3mg measure 9am serum cortisol and ACTH

Cortisol <100nmol/L or <150nmol/L and ACTH <10pg/mL
  - Inhaled, nasal or topical – start HC replacement, ask referral team to adjust GC dose, sick day rules
  - Oral, intra-articular or intra-muscular – ask referral team to adjust GC dose, sick day rules, rescue steroids

Cortisol 100nmol/L (or 150nmol/L & ACTH >10pg/mL) – 350nmol/L
  - im or iv 250µg Synacthen test
  - 30min se cortisol >550nmol/L
    - No
    - Yes

Cortisol >350nmol/L
  - No change unless symptoms of AI
Sick Day Rules

• Extra steroid cover during acute illness, trauma or surgery

• Double the normal daily steroid dose when patient has a temperature > 37.5°C

• If vomits/diarrhoea should take 5mg prednisolone equiv immediately after and sip electrolyte fluids

• Severe illness (temp > 40°C or repetitive vomiting / diarrhoea) ask for medical help, administer 100mg HC im and hospital assessment

• Steroid cover is needed in surgery and labour
“Addisonian” Emergency Crisis

• Immediate samples for cortisol and ACTH

• Intravenous N. Saline

• Hydrocortisone 100mg im 6 hourly until eating and drinking
(Both saline and HC as soon as blood test taken – do not wait for result)

• Treat precipitant e.g infection

• When resolving convert to double oral steroid dose for 2 to 3 days, then back to normal treatment
Conclusion

• Steroids are highly effective drugs, essential and life saving

• Unfortunately they can result in side effects impacting on patient health and quality of life

• Careful monitoring for adverse effects, prophylactic measures and early treatment may reduce patient morbidity

• When in doubt about HPA status refer patient to endocrinology