Is there a safe and effective way to wean patients off long-term corticosteroids?

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Overview

- Approach to corticosteroid therapy
- Definition of ‘long term use’
- Challenges of deprescribing
  - HPA suppression
  - Psychological dependence
  - Physical dependence without HPA suppression
- Topical corticosteroids
Corticosteroid therapy

Aim:
- Maximum possible therapeutic benefit with least possible cumulative dosage to minimise adverse effects

Approach:
- Treat until disease is controlled (or not despite adequate trial)
- Withdraw steroids without reactivating disease or causing withdrawal reactions
Indications

- Pulmonary
  - Asthma/COPD
  - Sarcoid
  - Pneumonitis

- Gastrointestinal
  - Inflammatory bowel disease
  - Chronic active hepatitis

- Blood
  - Haemolytic anaemias
  - Immune thrombocytopenic purpura
  - Leukaemia, lymphoma (with chemotherapy)

- Skin
  - Dermatitis
  - Pemphigus

- Musculoskeletal
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Myositis
  - Polyarteritis
  - Polymyalgia rheumatica

- Renal
  - Nephrotic syndrome
  - Graft versus host disease

(~1-3% adults)
Adverse effects

- Increased appetite
- Weight gain
- Insomnia
- Emotional lability
- Cushingoid
- HPA suppression
- Impaired wound healing
- Myopathy
- Osteonecrosis
- Increased susceptibility to infections
- Diabetes mellitus
- Acne
- Hypertension
- Peptic ulcer
- Hypokalaemia
- Atherosclerosis
- Cataracts
- Fatty liver
- Osteoporosis
- Skin atrophy
- Growth retardation

HPA – hypothalamic pituitary adrenal axis

Susceptible patients

Challenges of corticosteroid (CS) withdrawal

- CS dose
- CS side effects
- Disease
- Withdrawal symptoms
- Adrenal insufficiency

Physiological dose
Hypothalamic-pituitary-adrenal axis (HPA) suppression

- Suppression detectable after a few days
- Atrophy of the corticotrophin cells of the anterior pituitary
- Adrenal atrophy
- Suppression may last for 6-12 months after cessation of external glucocorticoids
- May never recover after very long term therapy

Other corticosteroid dependence

- ‘Glucocorticoid withdrawal syndrome’
  - Symptoms of apparent adrenal insufficiency despite normal HPA function and lack of disease recrudescence
  - Can occur when still receiving supraphysiological doses of corticosteroids
  - Mechanisms?
    - Tissue dependence on supraphysiological concentrations of glucocorticoids
    - Relative glucocorticoid resistance
  - Can be self-limiting – median duration 10 months

- Psychological dependence
  - ‘vigorous insistence on corticosteroids out of proportion to objective signs and symptoms of inflammation’
Symptoms

**Adrenal insufficiency**
anorexia, fatigue, nausea, vomiting, dyspnea, fever, arthralgia, myalgia, and orthostatic hypotension, dizziness, fainting, circulatory collapse

**‘Glucocorticoid withdrawal syndrome’**
anorexia, nausea, emesis, weight loss, fatigue, myalgias, arthralgias, weakness, headache, abdominal pain, lethargy, postural hypotension, fever, skin desquamation, tachycardia, emotional lability, delirium, psychotic states

Distinguishable only by HPA testing
Long term corticosteroid use

- Sufficient duration to have caused ‘dependence’
  - HPA axis suppression unlikely
    - <3 weeks, alternate day prednisolone <10 mg
  - HPA axis suppression likely
    - Cushingoid
    - >20mg prednisolone >3 weeks
    - Evening dose prednisolone >5mg more than a few weeks
  - HPA axis suppression uncertain
    - 10-20mg prednisolone/day >3 weeks
    - <10 mg prednisolone/day for more than a few weeks
Started prednisolone for polymyalgia rheumatica 2014
- Dose increases for COPD exacerbations 3-4 x/year
- R Colles fracture 2017, vertebral fractures 2018, 2019
- Currently taking prednisolone 12mg/day
  - lowest dose in 2019 5mg/day
    - aches and pains, worsening breathlessness
    - faint, dizzy and fatigued
- Other medication – adcal D3 one bd, alendronic acid 70mg ow, fostair 100/6 2 puffs bd, tiotropium (handihaler) 18 micrograms od
Q1. How would you manage her long term steroid use?

1. Perform a low-dose ACTH stimulation test before changing treatment (55%)
2. Reduce prednisolone by 1mg/day every 2-4 weeks to 5mg/day (45%)
3. Reduce prednisolone by 2.5mg/day each month to stop (0%)
4. Start methotrexate and reduce prednisolone by 1mg/day per month to stop (0%)
5. Switch to equivalent dose hydrocortisone for long term adrenal replacement (0%)
## Steroid taper – rule of thumb

<table>
<thead>
<tr>
<th>Dose (prednisolone or equivalent)</th>
<th>Taper</th>
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</thead>
<tbody>
<tr>
<td>&gt;40 mg</td>
<td>5-10mg/day every 1-2 weeks</td>
</tr>
<tr>
<td>20-40mg</td>
<td>5mg/day every 1-2 weeks</td>
</tr>
<tr>
<td>10-20mg</td>
<td>2.5mg/day every 2-3 weeks</td>
</tr>
<tr>
<td>5-10mg</td>
<td>1mg/day every 2-4 weeks</td>
</tr>
<tr>
<td>≤5mg</td>
<td>0.5mg/day every 2-4 weeks (alternate daily doses e.g. 4mg/5mg)</td>
</tr>
</tbody>
</table>
What to do about withdrawal failure

- **Disease reactivation**
  - Check diagnosis – specialist input
  - Try steroid sparing agents
  - Wean to lowest dose that controls symptoms
    - Mild symptom flare, wait 7-10 days, pain control
    - True disease flare increase dose by 10-15%
    - If no better, double dose
  - Resume wean once symptoms reduced

- Rheumatology – no real basis for diagnosis
- COPD – not an indication for long term steroids – try azithromycin
What to do about withdrawal failure

- Symptoms suggestive of HPA axis suppression
  - Consider testing/endocrine input

  Wean to 5mg
  Endocrinology referral
HPA axis suppression

**Diagnosis**
- Test patients on ≤5mg prednisolone who can’t reduce dose further due to non-disease related symptoms
- Early morning cortisol +/- short synacthen test
  - Prednisolone cross-reacts (30%) with cortisol assays
  - Withhold for 24 hours or switch to dexamethasone before testing
HPA axis suppression

Management
- Mild to moderate adrenal suppression
  - Slow wean, repeat testing
- Severe adrenal suppression
  - Long term glucocorticoid replacement with lowest dose at which they feel well e.g. 3mg prednisolone
  - Consider changing to hydrocortisone (possibly less adverse effects on bone)

Sick day rules to prevent adrenal crisis
- [https://www.addisonsdisease.org.uk/newly-diagnosed-sick-day-rules](https://www.addisonsdisease.org.uk/newly-diagnosed-sick-day-rules)
What to do about withdrawal failure

- If no HPA suppression
  - Non-specific withdrawal symptoms
    - Slow taper, symptom management e.g. with NSAIDs
  - Psychological dependence
    - Other support e.g. counselling, hospice
    - Consider antidepressants
Q2. Which patient is most likely to develop adrenal suppression?

1. 22-yr-old woman with flexural eczema prescribed hydrocortisone cream 0.5% & Gedarel® 30/1502 PO
   - 5.56%

2. 28-yr-old man with atopy and nasal polyps prescribed mometasone nasal spray 50 micrograms each nostril od and fexofenadine PO 120mg daily
   - 11.11%

3. 35-yr-old woman with asthma and ABPA prescribed Flutiform® 501 2 puffs bd and itraconazole 200 mg od
   - 55.56%

4. 54-yr-old man with bilateral uveitis and sarcoidosis prescribed dexamethasone 0.1% eye drops 4 hourly
   - 11.11%

5. 66-yr-old woman with chronic otitis externa prescribed prednisolone 0.5% ear drops 2-3 every 2-4 hours and tamoxifen 20mg PO od
   - 16.67%

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1. Fluticasone 50, formoterol 5
2. Ethinylestradiol 30 micrograms, Desogestrel 150 micrograms
### Pharmacodynamics

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Relative glucocorticoid receptor binding affinity</th>
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<tbody>
<tr>
<td>Fluticasone furoate</td>
<td>2989</td>
</tr>
<tr>
<td><strong>Mometasone furoate</strong></td>
<td>2100</td>
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<tr>
<td>Fluticasone propionate</td>
<td>1775</td>
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<tr>
<td>Beclomethasone dipropionate (BMP)*</td>
<td>1345</td>
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<tr>
<td>Ciclesonide (des-CIC)*</td>
<td>1200</td>
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<tr>
<td>Budesonide</td>
<td>935</td>
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<tr>
<td>Triamcinolone acetonide</td>
<td>233</td>
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<tr>
<td>Flunisolide</td>
<td>190</td>
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<tr>
<td><strong>Dexamethasone</strong></td>
<td>100</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>12</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>~2.5</td>
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</table>
Pharmacokinetics

- Absorption
- Distribution
- Metabolism
- Excretion
- Side effect
- Effect

Topical

- Epithelial quality
- Surface area
- Dosage
- Formulation

Corticosteroid-binding globulin

Oestrogens

Itraconazole

HIV drugs
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Summary

- Aim: maximum disease control, minimum cumulative dosage
- Start to withdraw steroids as soon as disease is controlled (or not after adequate trial)
- Long term therapy for >3 weeks can cause dependence
  - HPA axis suppression, glucocorticoid withdrawal syndrome, psychological dependence
- Taper long term treatment to minimise risk of disease recurrence and withdrawal effects
- Consider endocrinology input for withdrawal failure of prednisolone ≤5mg to distinguish HPA suppression from other reactions