Corticosteroids-benefits and risks

Katherine Webber
Introduction

- Definition and pharmacology
- Different steroids
- Uses
- Risks/ side-effects
Objectives

• To be able to advise when steroid use is indicated in palliative patients
• To be able to counsel and recognise steroid-related side effects
• To be able to safely stop steroids
Steroids (Crouching Tiger Hidden Gabber Megamix)

EP by Death Grips

Released May 22, 2017

Genre Experimental hip hop • digital hardcore
Definition

- A steroid is a biologically active organic compound (17 carbon atoms) bonded in four rings arranged in a specific molecular configuration.
Steroids

- Steroids vary by the functional group attached and the oxidative state of the rings
- Major classes endogenous steroids
  - Corticosteroids
    - Glucocorticoids (Cortisol)
    - Mineralocorticoids (Aldosterone)
  - Sex steroids
    - Progesterone, Androgens, Oestrogens
Glucocorticoid mechanism of action
Physiological functions

• ‘act to maintain homeostasis in the face of stressful stimuli’
  – Anti-inflammatory
  – Immunomodulatory
  – Development of lung and nervous systems
  – Skeletal growth
  – Behaviour
  – Metabolism-gluconeogenesis, insulin resistance
Feedback regulation of glucocorticoid

- Basal hormone levels follow a circadian rhythm
- Circadian lowering is physiologically necessary
Synthetic corticosteroids

- Betamethasone acetate
- Betamethasone phosphate
- Dexamethasone
- Hydrocortisone
- Prednisolone
- Prednisone
Pharmacodynamics

<table>
<thead>
<tr>
<th>Category</th>
<th>Medication</th>
<th>Potency</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short acting</td>
<td>Cortisol</td>
<td>1.0</td>
<td>20mg</td>
</tr>
<tr>
<td></td>
<td>Prednisolone</td>
<td>4.0</td>
<td>5mg</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
<td>5.0</td>
<td>4mg</td>
</tr>
<tr>
<td>Intermediate acting</td>
<td>Triamcinolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long acting</td>
<td>Dexamethasone</td>
<td>30</td>
<td>0.75mg</td>
</tr>
</tbody>
</table>
Question

• Raise your hand if you have prescribed or recommended corticosteroid therapy in the last week?
Benefits ??

• Appetite
• Fatigue
• Oncological problems (lymphangitis/MSCC/Brain mets)
• Nausea and vomiting
• Pain
Cancer Pain

• Vecht et al.
  – 10mg vs 100mg Dexamethasone MSCC
  – Pain reduced significantly
    • 3 hours (5.2 to 3.8)
    • 24 hours 2.8
    • 1 week 1.4
Cochrane review

• Haywood et al.
  – Improvement in pain intensity at 1 week but not sustained beyond this
  – Heterogeneous patient group
<table>
<thead>
<tr>
<th>Study</th>
<th>Target population</th>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basile 2012</td>
<td>Bone neoplasm</td>
<td>Dexamethasone</td>
<td>4 mg/mL</td>
</tr>
<tr>
<td>Bruera 1985</td>
<td>Advanced cancer</td>
<td>Methylprednisolone</td>
<td>32 mg</td>
</tr>
<tr>
<td>Bruera 2004</td>
<td>Advanced cancer</td>
<td>Dexamethasone</td>
<td>20 mg</td>
</tr>
<tr>
<td>Della 1989</td>
<td>Advanced cancer</td>
<td>Methylprednisolone</td>
<td>125 mg</td>
</tr>
<tr>
<td>Fossa 2001</td>
<td>Prostate cancer</td>
<td>Prednisone</td>
<td>20 mg</td>
</tr>
<tr>
<td>Graham 2006</td>
<td>Malignant spinal cord compression</td>
<td>Dexamethasone</td>
<td>16 mg</td>
</tr>
<tr>
<td>Graham 2006</td>
<td>Malignant spinal cord compression</td>
<td>Dexamethasone</td>
<td>96 mg</td>
</tr>
<tr>
<td>Lauretti 2013</td>
<td>Advanced cancer</td>
<td>Dexamethasone</td>
<td>10 mg</td>
</tr>
<tr>
<td>Lee 2008</td>
<td>Multiple myeloma</td>
<td>Dexamethasone</td>
<td>40 mg</td>
</tr>
<tr>
<td>Mercadante 2007</td>
<td>Adjuvant drug in advanced cancer patients</td>
<td>Dexamethasone</td>
<td>8 mg</td>
</tr>
<tr>
<td>Paulsen 2014</td>
<td>Advanced cancer</td>
<td>Methylprednisolone</td>
<td>16 mg</td>
</tr>
<tr>
<td>Popiel 1989</td>
<td>Advanced cancer</td>
<td>Methylprednisolone</td>
<td>125 mg</td>
</tr>
<tr>
<td>Teshima 1996</td>
<td>Bone metastases</td>
<td>Methylprednisolone</td>
<td>500 mg</td>
</tr>
<tr>
<td>Twycross 1985</td>
<td>Breast or bronchus cancer</td>
<td>Prednisolone</td>
<td>15 mg</td>
</tr>
<tr>
<td>Vecht 1989</td>
<td>Advanced cancer</td>
<td>Dexamethasone</td>
<td>10 mg</td>
</tr>
<tr>
<td>Vecht 1989</td>
<td>Advanced cancer</td>
<td>Dexamethasone</td>
<td>100 mg</td>
</tr>
<tr>
<td>Yennurajalingam 2013</td>
<td>Advanced cancer</td>
<td>Dexamethasone</td>
<td>8 mg</td>
</tr>
</tbody>
</table>
Analysis 1.1. Comparison 1 Pain, Outcome 1 Pain at 1 week.

Review: Corticosteroids for the management of cancer-related pain in adults

Comparison: 1 Pain

Outcome: 1 Pain at 1 week

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Drug N</th>
<th>Mean (SD)</th>
<th>Control N</th>
<th>Mean (SD)</th>
<th>Mean Difference</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basile 2012</td>
<td>12</td>
<td>1.5 (0.7)</td>
<td>8</td>
<td>2.9 (0.6)</td>
<td></td>
<td>26.1 %</td>
</tr>
<tr>
<td>Bruera 1985</td>
<td>28</td>
<td>3.68 (1.4)</td>
<td>28</td>
<td>5.01 (1.5)</td>
<td></td>
<td>21.4 %</td>
</tr>
<tr>
<td>Yennunjaliningam 2013</td>
<td>43</td>
<td>3.95 (2.89)</td>
<td>41</td>
<td>5.01 (2.8)</td>
<td></td>
<td>12.9 %</td>
</tr>
<tr>
<td>Bruera 2004</td>
<td>22</td>
<td>2.4 (3.4)</td>
<td>21</td>
<td>2.8 (3.6)</td>
<td></td>
<td>5.7 %</td>
</tr>
<tr>
<td>Mercadante 2007</td>
<td>34</td>
<td>3.1 (1.9)</td>
<td>31</td>
<td>3.2 (1.9)</td>
<td></td>
<td>17.8 %</td>
</tr>
<tr>
<td>Paulsen 2014</td>
<td>25</td>
<td>3.6 (1.96)</td>
<td>22</td>
<td>3.68 (1.56)</td>
<td></td>
<td>16.2 %</td>
</tr>
</tbody>
</table>

Total (95% CI) 164 151

Heterogeneity: Tau^2 = 0.21; Chi^2 = 9.72, df = 5 (P = 0.08); I^2 = 49%

Test for overall effect: Z = 3.03 (P = 0.0024)
Test for subgroup differences: Not applicable
Corticosteroids for pain control

- Data for 1 week
- Majority administered for 1 week and then stopped
- Dexamethasone dose 8mg minimum
- No comparative data regarding dosing or steroid type
- Seems well tolerated
Nausea and vomiting (not related to chemotherapy)

Figure 4. Forest plot of comparison: I Nausea, outcome: I.1 Nausea at 8 days.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Dexamethasone Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yennuraijalingam 2013</td>
<td>-1.18</td>
<td>2.91</td>
<td>43</td>
<td>-0.45</td>
<td>2.81</td>
<td>41</td>
<td>73.4%</td>
<td>-0.73 [-1.95, 0.49]</td>
<td></td>
</tr>
<tr>
<td>Bruera 2004</td>
<td>5.9</td>
<td>3.6</td>
<td>22</td>
<td>5.7</td>
<td>3.2</td>
<td>21</td>
<td>26.8%</td>
<td>0.20 [-1.83, 2.23]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>65</strong></td>
<td><strong>62</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>-0.48</strong></td>
<td><strong>[-1.53, 0.57]</strong></td>
<td><strong>-0.48</strong></td>
<td><strong>[-1.53, 0.57]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00$; $\text{Chi}^2 = 0.59, \text{df} = 1 (P = 0.44), I^2 = 0\%$
Test for overall effect: $Z = 0.90 (P = 0.37)$

Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery) (Review)
Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Fatigue

- Meta-analysis
- Tomlinson et al.
- No association with improvement in fatigue

<table>
<thead>
<tr>
<th>Corticosteroids</th>
<th>Inoue et al., 2003</th>
<th>Zarger-Shoshtari et al. 2009</th>
<th>Yennurajalingam et al., 2013</th>
<th>Paulsen et al., 2014</th>
<th>Eguchi et al., 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>28–78</td>
<td>&gt;1 Type</td>
<td>34–92</td>
<td>29–89</td>
<td>NR</td>
<td>46–84</td>
</tr>
<tr>
<td>On therapy</td>
<td>No</td>
<td>On therapy</td>
<td>Both</td>
<td>Both</td>
<td>Off therapy</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Yes</td>
<td>Dexamethasone</td>
<td>Methylprednisolone</td>
<td>No</td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
<td>Placebo</td>
</tr>
</tbody>
</table>
Anorexia-cachexia

- Very limited data
- Some benefit in small studies
- Other drugs have better evidence and fewer side effects
Side effects

• Related to multiple systems (Clinical studies 1 week)
  – Restlessness and sleeplessness
  – Cushingoid face
  – Anxiety
  – Fluid retention
  – Hyperglycaemia
Side effects

• Long term
  – Suppression of ACTH
  – Immunosuppression
  – GI bleeding and pancreatitis
  – Weight gain and fat redistribution
  – Osteoporosis
  – Myopathy
Steroid side effects/ toxicity

• Directly correlates with dose and duration
• Studies evaluating high dose (100 mg/day) versus intermediate dose (16mg/day) dexamethasone for MSCC found higher incidence of adverse events (30% versus 15%)
  – Perforated ulcer, mania, psychosis, hyperglycaemia, proximal myopathy
• Side effect incidence lower (5%) if treatment less than 3 weeks duration
Withdrawal from steroids

• Adrenal insufficiency
• Symptoms
  – Anorexia
  – Myalgia
  – Nausea/ vomiting
  – Lethargy
  – Headache
  – Fever
  – Arthralgia
  – Wt loss and postural hypotension
Adrenal insufficiency

• Can only be diagnosed with stimulation test
  – Injection of ACTH and then measure Cortisol level

• Dinsen et al. Systematic review
  – 46-100% of patients had abnormal ACTH test 24 hour after last steroid dose
  – 26-49% had insufficient response after 1 week
  – 20% at 6 months
  – 10% at 1 year
  – Correlates with clinical symptoms
Adrenal response dependent on dose
Stopping steroids

• Slow tapering is recommended but limited data to support this
• Most rational strategy if prolonged course would be to switch to hydrocortisone and taper individually
• Aim to reduce dose by 20% every 4 days until physiological dose achieved
• Advice about episodes of stress
• Steroid emergency card
Stopping steroids

• If on corticosteroids for oncological problem then need to stop within 2 weeks of starting
• Reduce by 20% every 4 days then stop
• If on corticosteroids for symptom issue need to weigh up benefits and risks
  – Prognosis
  – Symptom benefit
  – Usually can prescribe for 1 week, assess response and stop
Alternate day dosing

- Some rheumatology data to support dosing with Prednisolone alternate day
- Still have desired anti-inflammatory effect without consistent suppression of ACTH
Conclusion

• No good data to support treatment for fatigue and appetite with corticosteroids
• Small benefit for pain control after 1 week
• Significant side effects and long term problems with ACTH suppression
• Dexamethasone has most powerful anti-inflammatory effect but short lived