Evidenced-Based Prescribing of Corticosteroids in Hospice and Palliative Medicine

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Objectives

• Name three differences in the side-effect profiles of commonly prescribed steroids;
• Name the most commonly prescribed steroid, dosage, and duration for the treatment of painful bone metastases;
• Describe when gastroprotection is indicated and identify the odds ratio for gastrointestinal bleeding among various risk groups
• Describe the evidence for the use of corticosteroids in nausea, fatigue, and appetite stimulation
• Name at least two important areas of assessment for patients started on corticosteroids
Key Resources Utilized

- “The Use of Corticosteroids as Adjuvant Therapy for Painful Bone Metastases: A Large Cross-Sectional Survey of Palliative Care Providers”
- A survey of physician practice patterns regarding corticosteroid use collected in 2015 from 765 participating palliative care & hospice providers

Clinical Vignette #1: 62 y/o M with Lung CA

- Bone metastases to ribs and spine
- Prognosis several weeks to a couple of months with PPS 40%
- Currently on methadone 10mg TID with pain rating 6/10 and complaining of sedation
- Previously on MS Contin 120 BID and MSIR 30mg q2 H prn

Key Questions: Corticosteroids for Pain Relief

1. What patients are most likely to benefit?
2. What corticosteroid is most popular/effective?
3. What is the optimal daily dose?
4. How should the daily dose be divided?
5. What is the optimal treatment duration?
6. What is the optimal tapering strategy?
1. Conditions Associated with Pain Relief from Corticosteroids

- Bone metastases
- Bowel obstructions
- Brain metastases
- Neuropathic pain syndromes
- Abdominal/pelvic mass

<table>
<thead>
<tr>
<th>Incidence of Bone Metastases by Cancer</th>
<th>Cancer</th>
<th>New Cases (2008)</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>186,320</td>
<td>65-75</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>215,320</td>
<td>30-40</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>184,450</td>
<td>65-75</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>68,810</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>34,380</td>
<td>20-25</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>37,340</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Myeloma</td>
<td>19,920</td>
<td>75-95</td>
<td></td>
</tr>
</tbody>
</table>


Proposed Mechanisms of Pain Relief from Corticosteroids

- Reducing tissue concentrations of key inflammatory mediators including prostaglandins, leukotrienes, and cytokines
- Reducing tissue edema by decreasing vascular permeability
- Reducing electrical activity in damaged nerves
- Potential shrinkage of tumor masses in steroid-responsive neoplasms


Haywood Cochrane Review Examining Pain Relief from Corticosteroids in Advanced Cancer Patients 2015

<table>
<thead>
<tr>
<th>Summary of Findings for the Main Comparison (Adverse events)</th>
<th>Significant adverse events</th>
<th>Incidence of side effect</th>
<th>Original study</th>
<th>Controlled study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid control</td>
<td>5% (15 of 325)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control control</td>
<td>6% (12 of 185)</td>
<td></td>
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</tr>
</tbody>
</table>


**Percentage of Patients with Bone Metastases Prescribed Corticosteroids for Pain Control**

**Corticosteroids for Neural Pain**

- Reflex sympathetic dystrophy
- Small fiber polyneuropathies
- Paraneoplastic syndromes

- Reduce pain by decreasing spontaneous discharge in injured nerves
- Patient-dependent with wide variability in response with experts recommending an n-1 trial

Pharmacokinetics of Selected Corticosteroids

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Relative Anti-Inflammatory Activity</th>
<th>Relative Mineralocorticoid Activity</th>
<th>Equivalent Dose (mg)</th>
<th>Biologic Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
<td>1</td>
<td>20</td>
<td>8-12</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>0.8</td>
<td>5</td>
<td>12-36</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>4</td>
<td>0.8</td>
<td>5</td>
<td>12-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>12-36</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>25</td>
<td>0</td>
<td>0.75</td>
<td>24-72</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25-30</td>
<td>0</td>
<td>0.75</td>
<td>24-72</td>
</tr>
</tbody>
</table>


Evidence Supporting Dexamethasone

Benefits of Dexamethasone

- Longer half-life
- Less fluid retention
- Higher potency
- Possibly less nausea/vomiting

Benefits of Prednisone/Prednisolone

- Less Myopathy

Dexamethasone in Prostate Cancer

3. Determining the Optimal Dose for Pain Relief

The optimal dose for pain relief is typically determined based on patient response and individual needs. A common approach is to use a combination of corticosteroids to achieve maximum pain relief while minimizing side effects.

4. Dividing the Corticosteroid Dose

- Advantages of once daily dosing
  - Increased compliance
- Advantages of more frequent dosing
  - May be able to administer a smaller total daily dose
  - May have fewer side effects (gastritis)


5. Determining Treatment Duration

- Maximum pain relief appears to occur during the first 3 weeks.
- Evidence of benefit beyond 3 weeks unclear.

6. Selecting a Tapering Strategy

• Few evidence-based clinical trials comparing tapering strategies
• Less than 3 weeks of corticosteroid use can generally be stopped without any taper.
• Any signs of Cushingoid appearance are associated with hypothalamic-pituitary-adrenal (HPA) axis suppression.

Clinical Vignette #2: 65 y/o W with Ovarian CA

• Mets to liver and carcinomatosis with 15 cm ovarian mass
• Unable to tolerate any PO intake on admission with frequent emesis
• Previous antiemetics include haloperidol, ondansetron, prochlorperazine, promethazine without success
• Decreased bowel sounds but no obvious obstruction on abdominal CT scan

Key Questions: Corticosteroids for Nausea

7. What patients are most likely to benefit from using corticosteroids for nausea?
8. What corticosteroid is the most commonly used and effective for nausea?
9. What is the optimal daily corticosteroid dose for nausea?
10. What is the optimal treatment duration for nausea relief?
7. Conditions Potentially Associated with Nausea Relief from Corticosteroids

- Chemotherapy induced nausea
- Malignant bowel obstruction
- Abdominal and pelvic mass
- Liver capsular distention
- Increased intracranial pressure

- Hypothesized mechanisms include:
  - Depletion of gamma-aminobutyric acid (GABA) in the medulla
  - Reducing the permeability of the blood-brain barrier to toxins
  - Inhibition of enkephalin release in the brainstem
  - Mass reduction from the anti-inflammatory effects relieving peripheral autonomic stretch receptors


Prevalence of Nausea in Advanced Illness

- Systematic Review - Less than originally thought
  - 43-49% HIV
  - 30-43% End stage renal disease
  - 17-48% End stage cardiac disease
  - 6-68% Cancer patients
  - COPD (inconclusive)

- Tends to cluster with fatigue, anorexia, drowsiness, and dyspnea


Determine the Etiology

- Disease related – uremia, edema of GI tract, liver mets
- Metabolic/chemical – medications, electrolytes
- Gastroparesis
- Constipation
- Bowel obstruction
- Vestibular
- Visceral
- Cortical (pain/anxiety/memories)
- Cranial (brain mets)

Single agent successful – 2/3rds
Multiple agents – 1/3rd
Pathophysiology – Mechanistic Approach

Most Common Etiologies of Nausea

- Chemical/metabolic – (30-40%)
  hypercalcemia, uremia, hyponatremia, drugs,
  chemo, renal and liver failure
  - mediated by CMTZ
  - treat with haloperidol, prochlorperazine, chlorpromazine,
    olanzapine
- Gastroparesis (35-45%)
  - mediated by dysfunction of autonomic NS
  - treat with metoclopramide

Treatment Options

- Gastroparesis – Metoclopramide (Reglan)
- Chemical – Halopenol/5HT3 antagonists (Zofran)
- Bowel Obstruction – Dexamethasone + Octreotide +
  Hyoscine
- Vestibular – Meclizine, Scopolamine
- Visceral – Dexamethasone
- Cortical – Benzoazepines
- Cranial – Dexamethasone
- Unclear – Prochlorperazine/Haloperidol
8. Selecting the Corticosteroid for Relief of Nausea

- Standard in many current chemotherapy regimens
- May be associated with lower rates of nausea in specific populations when compared to other corticosteroids
- Used in the few clinical trials evaluating corticosteroids for relief of nausea

9. Selecting the Dosage for Relief of Nausea

- Most indications: 0.5-8 mg total daily dose administered once or twice daily
- Malignant bowel obstruction: 6-16 mg
- Elevated intracranial pressure: 4-16 mg daily (loading dose of 10 mg may be used)

10. Optimal Treatment Duration for Nausea Relief

- The shorter the better with corticosteroid discontinuation within 7-10 days if no response

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8/26/2016
11. Managing Fatigue, Anorexia, and Quality of Life with Corticosteroids (1/2)

- Short burst of 7 days of 16mg of methylprednisone BID vs placebo
- Outcomes measured using the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire C30
- Fatigue: improvement of 17 points in corticosteroid group vs worsening of 3 in placebo group
- Appetite loss: improvement of 24 in corticosteroid versus loss of 2 in placebo group
- Patient satisfaction: 5.4 points vs 2.0 points in favor of corticosteroid group


11. Managing Fatigue, Anorexia, and Quality of Life with Corticosteroids 2/2

- Cancer patients randomized to either 4mg of dexamethasone or placebo for 14 days
- Outcomes including the Functional Assessment of Chronic Illness-Fatigue (FACIT) and the Edmonton Symptom Assessment Scale (ESAS)
- Fatigue improved in dexamethasone vs placebo (9 vs 3 points)
- QOL improved in dexamethasone vs placebo at day 15
- Lower ESAS physical distress scores in dexamethasone group
- No difference in frequency of adverse effects


Clinical Vignette #3: 74 y/o M with Prostate CA

- Vertebral and ischial bone metastases
- Pain poorly controlled but reluctant to increase opioids secondary to sedation
- Other major complaints include loss of appetite and severe fatigue
Key Questions: Corticosteroids in General

12. In which patients should gastroprotection be prescribed?
13. How do different methods of gastroprotection compare in efficacy and cost?
14. What are key components of the nursing assessment when starting corticosteroids?

12. Patients Most Likely to Benefit From Gastroprotection When Starting Corticosteroids

Major Risk Factors
- Patients with history of GI bleed/PUD
- Concurrent NSAID or aspirin use
- H. pylori infection
- Stress ulcer risk factors
  - Sepsis, MV, Coagulopathy, TBI, burns

Additional Risk Factors
- Comorbid Conditions
  - Cirrhosis, COPD, renal failure, organ transplant
  - Gastrinoma, CMV, HSV, Crohn’s disease, Sarcoid
- Other drug factors
  - Acetominophen, Anticoagulants, Clopidogrel, Selective serotonin reuptake inhibitors (SSRI), Alendronate, Potassium Cl, Spironolactone, Chemotherapy
- Structural issues - Duodenal obstruction, Gastric bypass surgery or antral exclusion
- Radiation therapy
Drug Class | Data for stress ulcer prophylaxis | Data for NSAID ulcer prevention | Pitfalls
--- | --- | --- | ---
Proton Pump Inhibitors (PPI) | • Meta-analysis of randomized trials comparing PPI to H2RA. Decrease rate of bleeding (OR 0.3, NNT 51) | Protective against ulcers/erosions (OR 0.35) | • C. Difficile (OR 1.7–1.9) • PNA (OR 1.12) • Rare CNS symptoms
H2 Receptor Antagonists (H2RA) | • Decrease overt bleeding (OR 0.29) | Standard dose not effective in preventing gastric ulcer; may prevent duodenal | • C. Difficile (OR 1.4) • PNA (OR 1.22) • Dose adjust renal failure • Rare CNS symptoms • Tachyphylaxis
Prostaglandin Analogs (Misoprostol) | • Small study showed similar effectiveness to IV Cimetidine | Possibly more effective than PPI but more drop out | • Diarrhea, nausea and abdominal pain • 200 mg QID dosing • Does not treat dyspepsia symptoms
Antacids | • Decrease overt bleeding (OR 0.4) | Not recommended | • Dosed every 1–2 hours • Ca, Mg, Phos abnormalities
Sucralfate | • Lowers bleeding, similar role to antacids | Not recommended | • Decreases drug absorption • SEID dosing • Constipation • Aluminum toxicity

13. How Different Methods of Gastroprotection Compare In Terms of Efficacy and Cost

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cost for 14 days of medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton Pump Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Omeprazole 20 mg</td>
<td>$9.18</td>
</tr>
<tr>
<td>Esomeprazole 20 mg</td>
<td>$9.84</td>
</tr>
<tr>
<td>Lansoprazole 15 mg</td>
<td>$10.67</td>
</tr>
<tr>
<td>Histamine Antagonists</td>
<td></td>
</tr>
<tr>
<td>Famotidine 10 mg (20 mg BID)</td>
<td>$8.75</td>
</tr>
<tr>
<td>Ranitidine 75 mg (150 mg BID)</td>
<td>$12.67</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Sucralfate tab 1 g (1 g BID)</td>
<td>$19.85</td>
</tr>
<tr>
<td>Misoprostol 200 mcg (200 mcg QID)</td>
<td>$67.18</td>
</tr>
</tbody>
</table>

Gastroprotection Summary

- Patients being treated with corticosteroids who have at least one other risk factor for PUD/GI bleed should be considered for gastroprotection.
- Once daily standard dose PPI, selected by cost-effectiveness of pharmacy formulary, is an acceptable strategy and H2RA may be a reasonable alternative. Risks of acid suppressing medications should not preclude use when indicated. Stop prophylaxis if risk factors resolve.
14. Key Components of the Nursing Assessment When Starting Corticosteroids

- Key questions to ask prior to starting corticosteroids include:
  - Any History of gastrointestinal bleeding or use of OTC medications (NSAIDs, aspirin, etc.)?
    - 4 fold risk in GI bleeding when on steroids with NSAIDs
  - History of diabetes/hyperglycemia?
  - What is patient’s prognosis?
  - Dose dependent and usually reversible once steroid stopped
    - 10-fold increased risk of requiring glucose lowering meds if on doses > Prednisone 30 mg or Dexamethasone 4.5 mg
  - Previous experiences with steroids?
    - If so, what type of reactions they have last time treated

Other Key Questions to Ask

- Other adverse reactions for patients on long term steroid use (longer prognosis) Many Hospice patients have already been on long term chronic use
  - Hypertension-increased risk especially for patients with uncontrolled or refractory
  - Cardiovascular disease-Higher risk for both heart failure and/or ischemic events. This risk increased if also on NSAIDS.
  - Osteoporosis-Increased risk of fractures increase significantly 3-6 months after starting. (Vertebral fractures most common)
  - Avascular necrosis-risk is low (less than 3%) in patients on <prednisone 15-20 mg/day and short term treatment. Risk increases with doses of prednisone >40mg/day for prolonged therapy >4 mos.

Additional Considerations with Corticosteroids

- Myopathy-patients taking >40-60 mg prednisone (6-9 mg dexamethasone) presents after a couple weeks and 2/3 of patients with brain tumors with dex continues after 3 months
- Skin changes-present in at least of 45 % of patients on steroids 3 months. (purpura, rash, acne)
- Fluid retention-less common with dexamethasone vs. prednisone. Contributes to HTN occurance
Other Adverse Reactions

- **Infections**
  - Affects on immune system (B-cells, T-cells, and Interleukins 1,2,6,8 and TNF). One Meta-analysis showed increased risk 1.5-8% depending on disease and doses of steroid. Other studies suggest 1-2X risk of infection.

- **Weight gain**
  - Increased appetite and fluid retention.
  - One study found weight gain in up to 70%, while another found increased appetite stimulation after 10 days in 46% on advanced COPD compared to 22% of controls.

- **Other Adverse Reactions**

- **Monitoring Patients on Corticosteroids**
  - Monitor for evidence of hyperglycemia.
    - Blood glucose baseline and periodically check in hospice. If diabetic, continue monitoring at patient’s current frequency.
    - Look for signs of thirst, lethargy, Amental status changes. Check baseline and periodically at time of hospice visit.
  - Urine output: polyuria, nocturia.
  - Insomnia
    - Have patient take steroids in am if possible and get sleep aid.
  - Mood changes are dose dependent.
    - One study prednisone 75 mg (12 mg dexamethasone) 30% hypomania and 10% depression after one week.
    - Assess for new onset or worsening signs of depression.
  - Psychosis
  - Vision changes
    - HSV corneal ulceration rare but require immediate discontinuation.
    - Cataracts also dose and duration dependent, more common if tx > 1 year.

Conclusions

- Corticosteroids may be a valuable therapeutic option for many common conditions in the hospice and palliative care setting but the benefits and burdens must be carefully examined.
- While few clinical trials have previously compared individual corticosteroids, dosages, treatment durations, or gastroprotective strategies, we now have important information on practice patterns that can be used to develop needed comparative effectiveness trials.
Questions?