GUIDELINE FOR THE USE OF CORTICOSTEROIDS FOR SYMPTOM MANAGEMENT IN ADVANCED CANCER (version 2)

Date written: September 2011
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1. Patient Group

Inclusion criteria: 1) Patients with a diagnosis of advanced cancer, in whom steroids have been prescribed for symptom management.
Exclusion criteria: 1) Patients with a diagnosis of advanced cancer receiving steroids in combination with chemotherapy or radiotherapy.
2) Patients with a non-malignant diagnosis.

2. Purpose of guideline

To promote the safe and appropriate prescription, administration and management of corticosteroids in patients accessing specialist palliative care services at Wigan and Leigh Hospice.

3. Disclaimer

This guideline has been registered with the Hospice. However, clinical guidelines are “guidelines” only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date.

4. Evidence base

There is extensive literature to support the safe use of corticosteroids in different clinical scenarios.
The grade of evidence to support these guidelines varies from 1a: Meta-analysis of randomised controlled trials to 5: Recommended best practice based on the clinical experiences of the guideline developer

5. Peer review

The guideline has been reviewed by the Quality Improvement Group (Clinical) at Wigan and Leigh Hospice.

6. Dissemination

The guideline will be available in the intranet clinical guidelines folder and in clinical guidelines folders situated in the Hospice. Details of the revised guideline will be added to the ward communication folder, and will be discussed in relevant team meetings. A copy of the guideline will be e-mailed to relevant members of staff.
7. Training

Training in the use of the guideline will be available to all clinical staff through the Wigan Borough Multidisciplinary Education Forum and other designated training sessions.

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9. Background

Within palliative medicine, there are several indications for the use of corticosteroids. Dexamethasone is the most frequently used corticosteroid due to relative potency, allowing reduced tablet burden, and due to the availability of a parenteral preparation. Dose used and duration of treatment varies according to indication. For each indication, the recommended dose of corticosteroid varies considerably within the literature.

Corticosteroids are known to cause a number of potential side effects, which must be weighed up against potential benefits. Side effects from steroids are dose specific. Although the short life expectancy of some patients with advanced cancer means they are unlikely to be affected by more long-term side effects, they can still experience significant symptoms related to corticosteroid use.

A survey by Hardy et al in 2001 stated, “the benefits of steroids when used according to defined guidelines were thought to outweigh toxicity.”
10. Management

a. Initiation - General Points

The indication for corticosteroid use should be documented clearly in the medical notes.\textsuperscript{2,3,14,15} A study by Gannon and McNamara in 2002 concluded that “though deemed “essential” the reason(s) for prescribing corticosteroids was only documented in two-thirds of cases”.\textsuperscript{16}

Corticosteroids cause decreased endogenous production of glucocorticoids and the degree of hypothalamic-pituitary-adrenal axis (HPA-axis) suppression depends on the dose and duration of therapy. In patients receiving large doses for longer periods, adrenal suppression may persist for up to 12 months.\textsuperscript{16}

There are known interactions between corticosteroids and other drugs and it is important to be aware of these and adjust doses accordingly. Refer to Appendix 1 and the British National Formulary\textsuperscript{17}.

- Always document indication clearly in notes\textsuperscript{2,3,14}
- Record potential drug interactions and appropriate dose adjustments\textsuperscript{17}
- Ensure patients are aware of common side effects, and the need to contact a health care professional if symptoms develop\textsuperscript{2,3,14}
- Where possible, give dexamethasone as a single dose in the morning. If a higher dose is needed, give in divided doses, the second being no later than 2pm, to minimise risk of sleep disturbance\textsuperscript{1-3,5,8,13,14,16}
- Document relevant information using the “Proforma for Corticosteroid Use” in SystmOne (this can be found in the IPU Templates Folder of the Clinical Tree)

b. Dose (based on indication)

The dose required for each indication varies considerably within the literature and often reflects personal experience of using corticosteroids. The following doses are recommendations and can be deviated from based on patient need.\textsuperscript{1-6}

<table>
<thead>
<tr>
<th>Indication</th>
<th>Total Daily Dose (Dexamethasone in mg)</th>
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<tbody>
<tr>
<td>Anorexia</td>
<td>2 – 4</td>
</tr>
<tr>
<td>General well-being</td>
<td>2 – 4</td>
</tr>
<tr>
<td>Weakness/Fatigue</td>
<td>2 – 4</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>4 – 8</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>4 – 8</td>
</tr>
<tr>
<td>Liver capsule pain</td>
<td>4 – 8</td>
</tr>
<tr>
<td>Nerve compression pain</td>
<td>4 – 8</td>
</tr>
<tr>
<td>Obstruction of viscus (bowel, bronchus, ureter)</td>
<td>8 – 16</td>
</tr>
<tr>
<td>Lymphangitis</td>
<td>8 – 16</td>
</tr>
<tr>
<td>Raised intracranial pressure</td>
<td>8 – 16</td>
</tr>
<tr>
<td>Spinal cord compression/Cauda equina compression</td>
<td>16</td>
</tr>
<tr>
<td>Superior vena cava obstruction</td>
<td>16</td>
</tr>
</tbody>
</table>
c. Gastric Protection

Use of preventive anti-ulcer therapy should be considered in patients receiving corticosteroids who are at risk of peptic ulcer formation.\textsuperscript{19} If gastrointestinal bleeding occurs, outcome can be poor due to poor performance status associated with advanced cancer.\textsuperscript{20} Most studies suggest that gastrointestinal bleeding is a rare complication of corticosteroid therapy when the patient is not taking any other medication that might increase risk of gastrointestinal irritation. Risk increases when there is concomitant use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs).\textsuperscript{19,26} Other drugs which may increase risk of gastrointestinal bleeding include bisphosphonates and selective serotonin re-uptake inhibitors.\textsuperscript{17}

- Consider gastric protection for all patients when initiating corticosteroids
- Prescribe gastric protection for all patients also taking aspirin or NSAIDs
- Initially use omeprazole 20mg daily or lansoprazole 15mg daily
- If patient already on preventive anti-ulcer therapy, or symptomatic, higher doses may be used\textsuperscript{8,17}

d. Steroid-induced Osteoporosis

There is limited research into the risk of corticosteroid-induced osteoporosis in patients with advanced cancer receiving corticosteroids for symptom management. The majority of research surrounds the use of prednisolone in lung disease and rheumatological disorders.\textsuperscript{27-33}

Most bone loss occurs within the first few months of treatment with steroids,\textsuperscript{30,34} therefore it is important to consider osteoporosis prophylaxis and lifestyle modifications when steroids are initiated. The effect of steroids on bone turnover is dose dependent and cumulative.\textsuperscript{35}

A number of bisphosphonates have been shown to reduce bone loss in patients on long-term corticosteroids, when used in conjunction with an adequate dietary calcium intake or additional calcium supplementation.\textsuperscript{27-33}

It is important to remember the non-pharmacological measures of improving bone mineral density or reducing loss.\textsuperscript{35-37}

\begin{itemize}
  \item Non-pharmacological/Lifestyle measures:\textsuperscript{35-37}
    \begin{itemize}
      \item Smoking cessation or avoidance
      \item Reduce alcohol consumption if excessive
      \item Regular weight bearing exercise if tolerated
      \item Well balanced diet rich in calcium
      \item Gait and balance assessment
      \item Falls prevention – assessment of home environment and review of medication which may increase risk of falls including sedatives and anti-hypertensives
    \end{itemize}
  \item Pharmacological measures:
    \begin{itemize}
      \item If prognosis longer than 3 months and corticosteroid treatment to continue for more than 3 months, discuss osteoporosis prophylaxis with patient\textsuperscript{17,27-37}
      \item Commence:
        \begin{itemize}
          \item Oral risedronate 35 mg weekly OR intravenous pamidronate 30 - 90mg every 3 months
          \item Calcium supplementation – Adcal D3 1 tablet twice daily (monitor calcium and phosphate levels)
        \end{itemize}
    \end{itemize}
\end{itemize}
If patients are receiving pamidronate or zoledronic acid intravenously for another indication, this will provide adequate prophylaxis.

e. Mouth Care

Candida and other fungal infections are a recognised side effect of corticosteroid use and monitoring is required whilst patients are taking corticosteroids.

- Monitor oral hygiene weekly whilst on corticosteroids
- Encourage good oral hygiene
- Treat suspected candida infection with nystatin 100000 units qds
- If oral candida persists, consider fluconazole 50mg od

f. Diabetes

The use of steroid treatment in people with pre-existing diabetes will result in worsening glucose control; this is termed **steroid-induced hyperglycaemia**. This warrants temporary additional and more active glycaemic management. A rise in glucose, related to steroid therapy occurring in people without a known diagnosis of diabetes is termed **steroid-induced diabetes**. This may or may not resolve when the steroids are withdrawn.  

The mechanisms leading to corticosteroid-induced diabetes in susceptible patients are multi-factorial, but include reduced uptake of glucose into cells and increased glucose production within the liver.  

Insulin resistance develops, resulting in post-prandial hyperglycaemia. Patients may be normoglycaemic overnight. The effect is dose dependent. Steroids administered as a single morning dose tend to cause a late afternoon or early evening rise in blood glucose levels, which can be managed with a morning sulphonylurea (e.g. gliclazide) or morning isophane insulin. Steroids given twice daily result in fluctuations in blood glucose levels at other times. Management of hyperglycaemia is more complex in this setting.  

For patients not known to be diabetic a random blood glucose checked prior to commencing steroids can identify those at risk of developing corticosteroid-induced hyperglycaemia.  

**Patient not known to be diabetic:**

- Check random capillary blood glucose (CBG) before starting corticosteroids.
  - a) If CBG <8.0mmol/L, manage as “Patient not at risk of corticosteroid-induced diabetes”
  - b) If CBG >8.0mmol/L, check random plasma glucose level
    - o If random plasma glucose level <7.8mmol/L, manage as “Patient not at risk of corticosteroid-induced diabetes”
    - o If random plasma glucose level between 7.8mmol/L and 11.0mmol/L, manage as “Patient at risk of corticosteroid-induced diabetes”
    - o If random plasma glucose level >11.0mmol/L, repeat random plasma glucose to confirm pre-existing diabetes not previously diagnosed, and manage as “Patient diabetic”

**Patient not at risk of corticosteroid-induced diabetes:**

- Monitor CBG on Days 1 & 2 of treatment, prior to evening meal
  - o If both readings <10mmol/L, repeat at Day 7. Discontinue monitoring if this reading is also <10mmol/L. If corticosteroid dose is increased, monitoring should be repeated
  - o If any readings >10mmol/L, manage as “Patient at risk of corticosteroid-induced diabetes”
Patient at risk of corticosteroid-induced diabetes:
- Monitor CBG daily, prior to evening meal
  - If repeated readings >15mmol/L (or urine glucose>2+), patient has corticosteroid-induced diabetes. Manage as "Patient diabetic"

Patient diabetic (both pre-existing and corticosteroid-induced):
- Monitor CBG regularly (at least once daily)
- Glucose target ranges for patients with a palliative diagnosis vary from those of the general population. Diabetes UK End of Life Care recommends:
  - No glucose level less than 6mmol/L
  - No glucose level higher than 15mmol/L
- Diabetes should be managed in line with Diabetes UK End of Life Diabetes Care recommendations (see appendix 2)

General points:
- When steroids are reduced, there is a risk of hypoglycaemia for patients using oral hypoglycaemic agents or insulin. This risk is particularly marked in the early morning. CBG must be monitored on a daily basis. Patients who are started on medication for corticosteroid-induced diabetes may no longer require this when corticosteroids are discontinued
- If a patient using medication to control diabetes experiences a deterioration in general condition, and oral intake is reduced, there is a risk of hypoglycaemia. CBG requires close monitoring

### g. Reduction/Discontinuation

The manufacturer's datasheet (SPC) for dexamethasone states that “Abrupt withdrawal of doses of up to 6mg daily of dexamethasone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression in the majority of patients.” Reduction and discontinuation of corticosteroids is based on the indication for the steroid, the dose, duration of use and likelihood of symptom relapse. It is important to consider a plan for review of corticosteroids and to document this in the medical notes.

#### Use of corticosteroids should be reviewed 5-7 days after initiation:
If commenced for raised intracranial pressure, spinal cord compression, superior vena cava obstruction, obstruction of viscus, lymphangitis:
- Reduce dose every 5-7 days
- Monitor for recurrence or worsening of symptoms

If commenced for other indication, assess benefit:
- If no benefit, discontinue after 5-7 days
- If benefit, reduce dose every 5-7 days to minimum effective dose

General points:
- The following patients should not have corticosteroids withdrawn abruptly, due to risk of HPA-axis suppression
  - patients taking corticosteroids for longer than 3 weeks
  - patients taking more than 6mg of dexamethasone daily
patients who have received a prolonged, or high dose course of corticosteroids in the preceding 12 months.16

- Any medications co-prescribed to prevent side effects should be stopped if corticosteroids are discontinued (i.e. gastric protection, osteoporosis prophylaxis).41
- Dose reductions should be recorded using the “Proforma for Corticosteroid Use” in SystmOne (this can be found in the IPU Templates Folder of the Clinical Tree)
- Ensure patient and other health care professionals involved in their care are aware of plans for reduction/discontinuation, by providing written guidance (TTO documentation, discharge letter or written instructions)

Reduction Regime:
- For doses over 8mg, reduce by 2-4mg every 5-7 days
- For doses 2-8mg daily, reduce by 2 mg every 5-7 days
- For doses less than 2 mg daily, reduce by 0.5-1 mg every 5-7 days
- Some patients require more gradual dose reduction – 500microgram dexamethasone tablets, or dexamethasone liquid can be used
- Monitor for symptom recurrence, and consider maintaining at lowest dose which controls symptoms

h. Last Days of Life

There is limited guidance around the discontinuation of corticosteroids at the end of life. It is usually appropriate to discontinue corticosteroids at this time, but all cases should be assessed individually.45 Corticosteroids may be continued if they have been needed to achieve good symptom control.41

- For patients unable to take oral medications, dexamethasone at doses of 8mg or less can be given as bolus subcutaneous injection.8,17
- If a continuous subcutaneous infusion is needed, dexamethasone should be administered via a separate driver to prevent precipitation
- Although there is no specific information available as to the relative potency of dexamethasone given via subcutaneous versus oral route, a 1:1 conversion is normally used.8

For further guidance or advice, please contact a member of the medical team:

Wigan and Leigh Hospice, Kildare Street, Hindley, Wigan. WN2 3HZ
Telephone: 01942 525566
11. References

1. Steroids in palliative care. GP notebook. Available at: http://www.gpnotebook.co.uk
2. Cambridge and Huntington Palliative Care Group. Use of Steroids in Palliative Care. Available at: http://www.arthurrankhouse.nhs.uk/
44. DermNet NZ. Systemic steroids. Available at: http://dermnetnz.org/treatments/systemic-steroids
# Appendix 1

## Common Drug Interactions with Corticosteroids

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<th>Drug</th>
<th>Comments</th>
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<td>Ciclosporin</td>
<td>Reduces plasma concentration of corticosteroids. Consider using higher than usual dose.</td>
</tr>
<tr>
<td>Barbiturates (<em>e.g.</em> phenobarbitol)</td>
<td>Enhance corticosteroid metabolism, therefore reducing plasma concentrations. Consider using higher than usual dose.</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Increases clearance of dexamethasone. Consider using higher than usual dose.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Enhances corticosteroid metabolism, therefore reducing plasma concentrations. Consider using higher than usual dose.</td>
</tr>
<tr>
<td>Macrolide antibiotics (<em>e.g.</em> clarithromycin, erythromycin)</td>
<td>Reduce glucocorticoid clearance. Consider using lower than usual dose to minimise side effects.</td>
</tr>
<tr>
<td>Thiazide (<em>e.g.</em> bendroflumethiazide, metolazone) and loop diuretics (<em>e.g.</em> furosemide, bumetanide)</td>
<td>Enhance potassium wasting effects of corticosteroids. Monitor potassium levels.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Corticosteroids can both enhance and diminish effects of oral anticoagulants. Monitor INR closely.</td>
</tr>
</tbody>
</table>
Algorithm for Managing Glucose taking Once Daily Steroid.42
(Adapted from Diabetes UK End of Life Diabetes Care (Version 2 10th July 2012))

End of Life Diabetes Management – Managing Glucose Control in Patients taking Once Daily Steroids

No known diabetes
- Check random glucose before starting on steroids to identify patients at risk.
- Random capillary glucose over 8mmol/L needs further checking with venous blood.
- Random venous glucose over 7.8mmol/L means at risk of developing diabetes with steroid therapy.
- Random venous glucose over 11mmol/L needs a second check to confirm pre-existing diabetes not previously diagnosed.

Known Diabetes (pre-existing or steroid induced)
- Reassess glucose control and current therapy.

Diet controlled or Metformin alone or metformin + gliptin
- Test before evening mealtimes.
- If develops repeated high readings (urine glucose>2+ or blood glucose >15mmol/L) add gliclazide 40mg with breakfast.
- Increase morning dose by 40mg increments.
- Aim blood glucose 6-15mmol/L or <1+/trace glycosuria before evening mealtimes.

Sulphonylurea treated (gliclazide)
- If no hypoglycaemia symptoms, day or night and taking less than 320mg/day.
  - Adjust balance of twice daily doses of gliclazide by giving up to a max 240mg morning dose (plus 80mg pm).
  - Aim blood glucose 6-15mmol/L or <1+/trace glycosuria before evening mealtimes.

Insulin controlled
- Twice daily insulin.
  - Morning dose will need to increase according to glucose reading before evening meal.
  - Aim blood glucose 6-15mmol/L before evening meal unless patient has "hypo" before meals despite snacks between meals.

Basal bolus insulin
- Breakfast & lunchtime rapid acting insulin may need to increase to avoid high readings before lunch or evening meal.
- Aim blood glucose 6-15mmol/L before lunch and evening meal unless patient has "hypo" before meals despite snacks between meals or has long gaps between meals.

Insulin dose adjustments
- Assuming no hypoglycaemia, pre meal time glucose is above 10mmol/L and increase in dose is needed.
  - Increase dose by 2-units if dose below 20units.
  - Increase dose by 5-10units if dose 20-50units.
  - Increase dose by 10-20units if dose 50-100units.
  - Review daily until stable, increasing dose as necessary.

If steroids are reduced or discontinued: review any changes made and consider reverting to previous therapy or doses.
If unsure at any stage about next steps or specific advice required on how to meet patient's needs or expectations, please contact the Community Diabetes Specialist Nurse Team – Tel: 01942 482234 Fax: 01942 482257.