International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

IJMRP

*Review Article*

# Use of Corticosteroids in Palliative Care Medicine: A Review

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## ABSTRACT

Corticosteroids are frequently prescribed to patients with advanced cancer for symptom relief. The indications are wide in this patient group ranging from treatment of specific conditions like spinal cord compression and raised intracranial pressure, to non-specific indications like anorexia, general weakness and other symptoms. The present review was done to study the use of corticosteroids in palliative care medicine.

**Keywords:** Corticosteroids, Palliative Care, Glucocorticoids.

**Article History:**

**Received:** 16-04-2021, Revised**:** 11-05-2021, Accepted**:** 27-05-2021

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| Access this article online | |
|---|---|
| Website: www.ijmrp.com | Quick Response code |
| DOI: 10.21276/ijmrp.2021.7.3.001 | |

## INTRODUCTION

Corticosteroids are a class of steroid hormones released by the adrenal cortex, which includes glucocorticoids and mineralocorticoids.[1] The term *steroid* applies to a wide range of molecules with varying physiological effects. More specifically, corticosteroids are a class of chemicals encompassing both laboratory synthesized and naturally produced hormones.[2] However, the term "corticosteroids" is generally used to refer to glucocorticoids. Named for their effect in carbohydrate metabolism, glucocorticoids regulate diverse cellular functions including development, homeostasis, metabolism, cognition and inflammation[3] & mineralocorticoids regulate sodium and water levels.[2] Due to their profound immune-modulatory actions, glucocorticoids are one of the most widely prescribed drugs in the world.[4] Glucocorticoids (cortisol in man and corticosterone in rodents) are steroid hormones synthesized and released by the adrenal glands in a circadian manner, in response to physiological cues and stress.[5]

## USE OF CORTICOSTEROIDS IN PALLIATIVE CARE MEDICINE

Corticosteroids have been shown to be effective for a variety of uses in the palliative care setting. As many as 50% of patients with advanced disease may be prescribed systemic corticosteroids during their illness.[6] The most commonly used systemic corticosteroids in clinical practice are prednisolone and dexamethasone. 40mg of prednisolone is equivalent to 6mg of dexamethasone.[7]

Dexamethasone is often selected in palliative care given its prolonged half-life, multiple routes of administration, and relatively low mineralocorticoid effect (thus less likelihood of fluid retention).[7] Prednisone, prednisolone, and methylprednisolone may be acceptable alternatives depending on the clinical circumstance. Prednisone is converted by liver enzymes to the active compound prednisolone. Therefore, prednisolone or methylprednisolone are preferred in liver impairment.[2] Topical and rectal preparations of corticosteroids are also available for treatment of local inflammation.[7]

## INDICATIONS FOR SYSTEMIC CORTICOSTEROIDS

- Anorexia[8-10]
- Bone pain[11,12]
- Dyspnoea[13]
- General well-being/ weakness[8,10,14]
- GI obstruction[14,15]
- Liver capsular pain[8]
- Lymphangitis carcinomatosis [16]
- Nausea[8,13]
- Neuropathic pain[6.,11,18]
- Post radiotherapy[18]
- Raised ICP[19,20]
- Spinal cord compression[21]
- SVCO/IVCO[22]
- Tracheal obstruction[23]

## GUIDELINES FOR USE OF CORTICOSTEROIDS

- It is important to limit the risk of inducing adrenal insufficiency. Therefore all patients prescribed corticosteroids should be given treatment for the shortest time using the lowest effective dose.[Level 1+] [24]
- The need for corticosteroids should be reviewed on a regular basis. [Level 3][8,13]
- Corticosteroids should be discontinued if there has been no clinical response within 5–7 days. [Level 4][11,13]
- Unless given in an emergency, corticosteroids should be administered once daily in the morning, or twice daily with the last dose before 2.00pm. This reduces suppression of the hypopituitary-adrenal axis and may prevent corticosteroid-induced insomnia. [Level 1+][24,25]
- In the event of a deterioration in the patient's symptom control, or the presence of an intercurrent illness, the corticosteroid dose may need to be increased for 5-7 days to maintain symptom control. Any subsequent reductions in dose may have to be made more slowly. [Level 4][26,27]
- All patients who are anticipated to require corticosteroids for longer than 3 weeks should be given a steroid card. [Level 4][24]
- The need for gastroduodenal cover with systemic corticosteroids is uncertain. A proton pump inhibitor or H2 antagonist should be co- prescribed with the corticosteroid for all patients taking NSAIDS[27] or those with two or more of the following risk factors. [Level 2+]
  - Advanced malignancy.
  - Previous history of peptic ulcer disease
  - Anticipated cumulative dose of corticosteroid equivalent to or greater than 140mg dexamethasone.[28]
- It may also be worth considering gastric protection for the following patients: [28,29] [Level 4]
  - Concurrent use of SSRIs, aspirin, anticoagulants, bisphosphonates.
  - Where the starting dose of corticosteroid is equivalent to or greater than 8mg dexamethasone.
- If a patient is taking anti-epileptics such as phenytoin, carbamazepine or barbiturates there is a¬ possibility of enzyme induction. Phenytoin in particular, has been shown to reduce the bioavailability of dexamethasone by as much as 75%. Patients may therefore require a 2-4 fold increase in their dexamethasone dose to achieve adequate symptom control.[30] Dexamethasone may also affect plasma phenytoin concentrations.[31] [Level 1-]

**Table 1: Dosage of Corticosteroids in Palliative Care[7,32,33]**

| Glucocorticoid | Dose Equivalent | Available Routes | Common Dosage |
|---|---|---|---|
| **Prednisone** | 4-6mg | PO | PO 5-40 mg/day in 1-2 doses |
| **Prednisolone** | 5mg | PO solution | 5-60mg/day in 1-2 doses |
| **Methyl-prednisolone** | 8mg | IV,IM,PO | 4-8mg/day in 1-2 dose |
| **Dexamethasone** | 0.75mg | PO,IV,IM,SQ | 2-8mg/day in 1-2 dose |

**Table 2: Suggested Starting Doses for Systemic Corticosteroids[29] [Level 4]**

| Suggested starting dose | Clinical indication | Mechanism of action |
|---|---|---|
| **2mg-4mg** | Anorexia General well-being | Uncertain |
| **4mg-8mg** | Nausea Dyspnoea | Uncertain |
| **8mg** | GI/GU obstruction Bone pain Neuropathic pain Liver capsule pain post-radiotherapy | Reduction of tumour oedema/ anti-inflammatory effect |
| **16mg** | Spinal cord compression Raised ICP SVCO/IVCO Tracheal obstruction Lymphangitis carcinomatosis | Reduction of tumour oedema/ anti-inflammatory effect |

## ADVERSE EFFECTS

Although the risk of adverse effects increases with dose and duration of any corticosteroid, long-term treatment (e.g. longer than a month) with relatively low doses (defined as a prednisone 5 mg or less) is generally well tolerated.[34]

- Early adverse effects (seen in days): hyperglycemia, fluid retention, and mental disturbances (insomnia, agitation, euphoria, paranoia).
- Late adverse effects (weeks to months): myopathy leading to proximal limb muscle weakness and reduced respiratory force; infection risk (especially fungal such as oral thrush); additive risk of GI bleed with NSAIDS.[35] Proton pump inhibitors and/or H2 antagonists are likely only needed for daily doses of ≥ 140 mg of dexamethasone or those taking concomitant NSAIDs.[28]

## CONSIDERATIONS WHEN PRESCRIBING CORTICOSTEROIDS

- Monitor regularly. Aim to discontinue corticosteroids within 5–7 days if there is an insufficient clinical response. Doing so can prevent the need to reduce the dose gradually (taper).
- Aim for the lowest therapeutic dose to prevent side effects. If taking ≤ 4 mg of dexamethasone (or its equivalent) for 3 weeks or less, it is likely safe to stop steroids abruptly without a taper.[34]
- Unless an emergency, most corticosteroids can be administered once daily in the morning, or twice daily with the last dose before 2:00 pm. This dosage schedule reduces suppression of the hypopituitary-adrenal axis and the risk of insomnia.

- Consider prognosis. Side-effects become a cumulative problem when prognosis is months or more.
- Monitor for hyperglycemia, especially in patients with an anticipated prognosis of months or more.
- Consult the primary oncologist before starting corticosteroids, as they may impact the effectiveness of immune-based systemic cancer treatments.[2]

## WITHDRAWAL OF CORTICOSTEROIDS

- Corticosteroids should be discontinued once symptoms have resolved or reduced to the lowest effective dose required to maintain symptom control.[24] [Level 1+]
- Any medications co-prescribed to prevent side effects should be stopped once corticosteroids have been discontinued.[29] [Level 4]
- The Committee on Safety of Medicines (CSM) has recommended that systemic corticosteroids should be gradually withdrawn in patients who have received treatment for longer than 3 weeks.[7,24,36] [Level 1+]
- Gradual withdrawal should also be considered in those patients who have received <3 weeks of treatment, but who are considered high-risk for developing adrenal insufficiency. [7,24,36] [Level 4]
- The CSM has recommended that systemic corticosteroids may be stopped abruptly in those whose disease: [7,24,36] [Level 1+]
  1. Is unlikely to relapse and
  2. Who have received treatment for less than 3 weeks and
  3. Who are not included in one of the high- risk groups
- Patients at high risk of developing adrenal insufficiency include the following: [7,24,36] [Level 4]
  1. Have recently received repeated courses of corticosteroids. (especially if taken for longer than 3 weeks)
  2. Are taking a short course of corticosteroids within one year of stopping long-term therapy.
  3. Have other possible causes of adrenal suppression.
  4. Have received more than prednisolone 40mg daily or the equivalent e.g. dexamethasone 4mg-6mg
  5. Have received repeat doses in the evening.
- If stopping steroids gradually, the dose may be reduced rapidly if symptoms allow, until a physiological level (7.5mg prednisolone / 1mg dexamethasone) is reached. This may involve halving the dose daily. The dose should subsequently be reduced more slowly to allow the adrenals to recover and to prevent a hypo-adrenal crisis. During the withdrawal of corticosteroids it is important to monitor the patient for deterioration of symptoms.[7,24,36] [Level 4]
- At the present time, dexamethasone 0.5mg tablets are in limited supply in the UK. Dexamethasone liquid is a suitable alternative.[36] [Level 4]
- If steroids are administered continuously via a syringe driver, the patient is at greater risk of adrenal insufficiency if the steroids are discontinued abruptly. In these circumstances, unless the patient is in the dying phase, corticosteroids should be withdrawn gradually.[24,29] [Level 4]

## CORTICOSTEROIDS IN THE LAST DAYS OF LIFE

- It is usually appropriate to discontinue corticosteroids in the dying phase unless they have been necessary in achieving good symptom control for the patient e.g. to treat: [Level 4] − headaches − seizures – pain[7,29]
- For patients unable to take oral dexamethasone, doses < 8mg may be given by bolus subcutaneous injection: [7,36][Level 4]
- If a continuous infusion is necessary, dexamethasone should be administered via a separate driver to prevent precipitation.[7,36]

## CONCLUSION

Corticosteroids are commonly prescribed in palliative care, often without guidelines. There is a high response rate to corticosteroid treatment and the results indicate that the positive effect can persist beyond four weeks. There is a need for implementation of guidelines based on solid evidence to assure patients optimal effect of corticosteroids and to minimize the risk for side effects.

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**Source of Support:** Nil. **Conflict of Interest:** None Declared.



**Cite this article as:** Rawaa Mahmoud Sulaiman, Sultan Ghazzay Alotaibi. Use of Corticosteroids in Palliative Care Medicine: A Review. Int J Med Res Prof. 2021 May; 7(3): 1-4.
DOI:10.21276/ijmrp.2021.7.3.001