Steroids as pain relief adjuvants

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Mr C. is a married, 80-year-old man with a straight posture and a sharp wit. Ten years ago he was diagnosed with a pancreatic carcinoid tumour and underwent a Whipple procedure. Since then, his symptoms have been well controlled with intermittent chemotherapy despite his known liver and multiple spinal metastases.

One year ago, Mr C. developed bony pain from his cervical spine disease and was started on hydromorphone. Despite escalating doses, he presents to your office with increasing pain. The pain is moderate in severity and described as aching and constant in his neck, with intermittent, sharp, shooting pain through his left upper back and shoulder. You consider adding a corticosteroid as an adjuvant analgesic to Mr C.'s hydromorphone regimen.

Steroids are among the most commonly used medications in palliative care. A Canadian study of ambulatory palliative care patients with cancer demonstrated that 40% of patients were receiving corticosteroids, and dexamethasone was the medication most commonly added by palliative care specialists.[1] This study echoes European studies in which corticosteroids were among the drugs most commonly prescribed by hospital-based palliative care services.[2-4]

There is evidence for the use of corticosteroids for specific indications, such as spinal cord compression,[5] raised intracranial pressure,[6] and bowel obstruction.[7] Corticosteroids are also commonly used for broader indications, such as to control pain, stimulate appetite, suppress nausea, and alleviate fatigue. However, there is little objective evidence in the literature for this broader use of corticosteroids.[2,8,9] This article will address the role of steroids in controlling pain as an adjuvant analgesic, a practice that is based primarily on expert opinion and empirical evidence.

Pain management

An adjuvant pain medication should be considered at all stages of the World Health Organization's pain ladder for mild to severe pain.[10] Mr C. shows evidence of mixed bony and neuropathic pain.[11] Steroids are particularly useful as adjuvant therapy for metastatic bone pain, neuropathic pain, and visceral pain.[12] As adjuvant agents, corticosteroids can directly reduce pain, reduce pain in concert with opioid use, allow for reduction of opioid dose, and have beneficial symptomatic effects outside of pain relief.

Glucocorticoids reduce pain by inhibiting prostaglandin synthesis, which leads to inflammation, and reducing vascular permeability that results in tissue edema. Glucocorticoids are also lipophilic molecules that can cross the blood-brain barrier. Research has shown that steroid receptors are found in the central and peripheral nervous systems and are responsible for growth, differentiation, development, and plasticity of neurons.[13] In particular, corticosteroids have been shown to reduce spontaneous discharge in an injured nerve, which reduces neuropathic pain.[12]

Dexamethasone is the most commonly prescribed corticosteroid for pain, but prednisone or prednisolone can also be used. An advantage of prednisolone is that the side effect of myopathy is less common. Dexamethasone causes less fluid retention than other steroids owing to the fact that it has less mineralocorticoid effect. It is also relatively more potent and, owing to dexamethasone's longer half-life, it can be taken once daily. The most appropriate dose of dexamethasone has not been determined, but a range of 2 to 8 mg orally or subcutaneously once to 3 times daily is generally accepted.

Side effects

Magnetic resonance imaging is completed to rule out spinal compression as a cause of Mr C.'s acute, severe pain. Results show progression of his bony disease, with some extension into his paravertebral musculature and no spinal cord impingement.

Through the spiritual care liaison and a family meeting, the anxiety among Mr C. and his family about his progressing disease was addressed.[14]

Mr C.'s pain is reduced to a 2 on a 10-point scale, with the addition of 8 mg/d of dexamethasone orally, titrated down over a few days to 4 mg/d orally. After a week of using 4 mg/d of dexamethasone, Mr C. reports that while he is feeling a lot better overall, he is sleeping poorly. From a discussion with Mr C., you come to the conclusion that the pain relief gained through the addition of dexamethasone is greater than the insomnia he is suffering as a side effect. You change his dexamethasone to morning dosing and prescribe 25 mg of trazodone orally once daily at bedtime to help with Mr C.'s insomnia.

Corticosteroids have a diverse side effect profile, and side effects are not uncommon; thus, the lowest

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effective dose should be used. Because side effects accumulate over the long term, corticosteroids are best used for short-term therapy (1 to 3 weeks).[8,11] In palliative care, corticosteroids are used for longer than 3 weeks for cases in which prognosis is in the short to medium term and side effects are unlikely to develop in the time remaining. For cases in which corticosteroids are used in the long term, their use should be monitored closely.[2] There is concern expressed in the literature that corticosteroids are not monitored closely enough in palliative care settings.[9]

The most frequently encountered side effects of dexamethasone are summarized in **Box 1**.[9,11,15] For cases in which side effects are mild or corticosteroids remain necessary to alleviate pain in the long term, medications can be prescribed to counteract side effects (eg, adjustment of diabetic medications to counteract hyperglycemia).[9] In patients at high risk of gastric bleed, gastroprotection can be prescribed concurrently with steroids. The combination of a nonsteroidal anti-inflammatory drug and a steroid increases the risk of gastric bleeding 15-fold; therefore, this combination should be avoided, particularly in the frail elderly.[16] For cases in which the use of steroids over many months is anticipated, a bisphosphonate can be considered concurrently in elderly patients and patients at risk of osteoporosis.

Box 1. Common side effects of dexamethasone

Most frequent side effects include the following:
- increased appetite or weight gain
- proximal muscle weakness
- insomnia
- gastrointestinal side effects
- psychiatric side effects, such as delirium, depression, anxiety, and psychosis
- osteoporosis with long-term use

Less frequent side effects include the following:
- infections
- hyperglycemia
- Cushing syndrome

Life-threatening side effects include the following:
- gastrointestinal bleeds
- thromboembolism

Data from Walsh et al,[9] Pereira,[11] and Sturdza et al.[15]

Of particular concern in palliative patients is the side effect of proximal muscle myopathy when added to the weakness from terminal illness. Acute steroid myopathy is rare and occurs with high-dose parenteral treatment in the first week of treatment. More commonly, myopathy occurs as an insidious process. The muscles of the lower limbs are affected first, and patients often complain of difficulty with stairs or rising from a chair as an early symptom. Fortunately, myopathy is most often reversible upon discontinuation of the steroid. Physiotherapy is also helpful.

In terms of drug interactions, anticonvulsants accelerate the metabolism of corticosteroids, and thus higher doses might need to be used in patients taking anticonvulsants. Corticosteroids might cause an increase or decrease in phenytoin and warfarin levels, and these should be monitored in patients on concurrent therapy. Live vaccines should not be given to patients taking corticosteroids owing to their impaired immune response.

After 3 months taking steroid therapy, Mr C.'s pain begins to escalate again. He reports that his pain in certain positions is now a 10 on a 10-point scale. Results of repeat magnetic resonance imaging show no spinal cord impingement, but there is further extension of his bony metastases. You urgently refer him to radiation oncology and titrate his hydromorphone and steroid accordingly in the meantime. Mr C. undergoes radiation therapy, and his pain is again reduced to a 2 on a 10-point scale. In addition to continued insomnia despite sedative treatment, Mr C. has noted that he feels weaker when using the stairs in his house and when rising from a chair. As his pain medication requirement has been reduced since his radiation therapy and he is suffering from both steroid-induced myopathy and insomnia, you and Mr C. together decide that it is time to taper him off his dexamethasone.

Discontinuing corticosteroid use

After 2 weeks of therapy with a steroid it can be discontinued without any adverse effects.[11] However, even low doses of corticosteroids can suppress the hypothalamic-pituitary-adrenal axis in the long term. Longer periods of treatment require a taper, the length of which depends on the duration of therapy.[15] The most appropriate method of tapering has not been determined in the literature.[17]

If patients have required steroids up to the last days of life and are no longer able to swallow, the steroids should be prescribed at full dose or tapered using the parenteral route (dexamethasone is available intravenously and subcutaneously) rather than abruptly stopping this medication.[8] If a stressful event, such as a serious infection or surgery, occurs within 1 week after discontinuation of steroid therapy, stress-dose steroid should be provided.

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It is important not to mistake withdrawal from corticosteroids for advancement of progressive disease in palliative care.[8] Withdrawal symptoms from corticosteroids include pain, nausea or vomiting, weight loss, depression, fatigue, fever, dizziness, and rebound symptoms that are unmasked when there is loss of symptom control once the corticosteroid is removed. Addisonian crisis is a life-threatening complication that can cause confusion, coma, cardiovascular shock, and even death. Notably in palliative patients, corticosteroid withdrawal is known to exacerbate terminal restlessness.

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Competing interests
None declared

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BOTTOM LINE

- Corticosteroids are among the most commonly used medications in palliative care. Their widespread use as analgesic adjuvants for bony, visceral, and neuropathic pain is widely supported by expert opinion.
- Corticosteroids reduce pain by reducing inflammation and edema associated with tumours and de polarization of damaged nerves.
- Dexamethasone is the most commonly used corticosteroid owing to its lack of mineralocorticoid effects, long half-life, and higher potency compared with other corticosteroids.
- Corticosteroids have many potential side effects that require frequent monitoring. Because most of these side effects manifest over the long term, corticosteroids are best used in the short term at the lowest effective dose.
- Discontinuing corticosteroids used for longer than 2 weeks should involve tapering to reduce the risk of steroid withdrawal. Worsening symptoms in this setting might be caused by steroid withdrawal, rather than progression of underlying disease.

POINTS SAILLANTS

- Les corticostéroïdes comptent parmi les médicaments les plus couramment utilisés en soins palliatifs. Leur utilisation généralisée comme adjuvants analgésiques dans les cas de douleur osseuse, viscérale et neuropathique est largement recommandée selon l'opinion d'experts.
- Les corticostéroïdes atténuent la douleur en réduisant l'inflammation et l'œdème associés aux tumeurs et à la dépolarisation des nerfs endommagés.
- La dexaméthasone est le corticostéroïde le plus fréquemment utilisé en raison de ses effets minéralocorticoïdes faibles, de sa longue demi-vie et de sa plus grande puissance par rapport à d'autres corticostéroïdes.
- Les corticostéroïdes ont de nombreux effets secondaires possibles qui exigent une surveillance fréquente. Parce que la plupart de ces effets secondaires se manifestent à long terme, les corticostéroïdes sont le plus indiqués à court terme et à la dose efficace la plus faible.
- La cessation des corticostéroïdes pris pendant plus de 2 semaines exige une diminution progressive pour réduire le risque des symptômes de sevrage des stéroïdes. L'aggravation des symptômes dans de telles circonstances pourrait être attribuable au sevrage des stéroïdes plutôt qu'à la progression de la maladie sous-jacente.