Neuro-Oncology Practice

*Neuro-Oncology Practice* 2(1), 6–12, 2015
doi:10.1093/nop/npu029
Advance Access date 9 October 2014

# Corticosteroid use in neuro-oncology: an update

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Because of the lack of curative approaches for most patients with malignant brain tumors, supportive therapy, which aims at maintaining quality of life and functional independence, has a central role in the treatment of many patients. Steroids are particularly important in the setting of supportive therapy. They are commonly used to treat tumor-associated edema, and their administration is typically associated with rapid symptom relief, such as the resolution of headaches. Besides their antiedema activity, corticosteroids are characterized by their potent antilymphoma properties and their effects against acute or delayed emesis caused by systemic chemotherapy in cancer patients. Accordingly, steroids are among the most frequently used drugs in oncology. These desirable properties of steroids are counterbalanced by cardiovascular, muscular, and psychiatric side effects. On the cellular level, corticosteroids exert various effects that translate into the desired clinical activity, but they also evoke significant toxicity that may outweigh the beneficial effects. The mode of action and the limitations of steroid treatment are summarized in this review article. Interactions between steroids and other drugs must be considered. A particular challenge to the ongoing use of glucocorticoids is that newer therapeutic approaches are being introduced in neuro-oncology for which concomitant steroids are likely to be contraindicated. These include the emergence of various immunotherapeutic approaches including vaccination strategies and treatment with immune checkpoint inhibitors. Since the administration of steroids may interfere with the activity of these novel therapies, an even more critical evaluation of their use will be required.

**Keywords:** brain tumor, corticosteroid, edema, mode of action, therapy resistance.

## Background

Corticosteroids are a class of biological mediators produced within the adrenal gland and synthesized from cholesterol. They are involved in the regulation of various processes such as metabolism, electrolyte regulation, inflammation, and stress responses. Based on their major effects, they are divided into two main groups: glucocorticoids and mineralocorticoids. Cortisol is the most prominent physiological mediator exerting glucocorticoid effects in humans, and aldosterone is the hormone with the strongest mineralocorticoid activity. Chemical modifications of the naturally occurring steroid hormones have resulted in the generation of numerous synthetic corticosteroids within the last 5 decades. Since then, these drugs have played a prominent role in the treatment of various pathological conditions and diseases. The glucocorticoid and mineralocorticoid activity of these synthetic drugs varies significantly. Accordingly, choosing the appropriate compound requires both anticipating the desired effect and carefully considering the potential side effects.

As outlined below in more detail, steroids are administered to brain tumor patients mainly to (i) reduce the tumor-surrounding edema and thereby the mass effect in the brain; (ii) target lymphomas in the CNS; and (iii) prevent or treat chemotherapy-induced nausea and vomiting. These effects are mediated by the glucocorticoid activity of steroids. The glucocorticoid and mineralocorticoid potency of some frequently administered corticosteroids are summarized in Table 1. The available compounds differ significantly in their duration of action. Because of its long half-life, which allows for administration of a single daily dose, dexamethasone has been the favorite drug for most indications. Furthermore, its strong glucocorticoid potency, associated with virtually absent mineralocorticoid effects, reduces the risk of electrolyte imbalances.

## Mode of Action

Glucocorticoids interact with the glucocorticoid receptor (GR), which is encoded by a gene located on chromosome 5.[1] The expression of the GR gene is under the control of at least 3 promoters, allowing for tissue-specific GR expression.[2] Because of alternative splicing as well as posttranscriptional and posttranslational modifications,

*Received 4 July 2014*

**Table 1.** Pharmacological properties of cortisol and synthetic glucocorticoids

| | Biological Half-life | Mineralocorticoid Potency | Glucocorticoid Potency | Recommended Daily Dose (range) | Cortisol Equivalent | Cushing Threshold |
|---|---|---|---|---|---|---|
| Cortisol (known as hydrocortisone when used therapeutically) | 8–12 h | 1 | 1 | (hydrocortisone: 20–30 mg) | 1 | 30 |
| Cortisone | 8–12 h | 0.8 | 0.8 | – | 1.25 | 40 |
| Prednisone | 12–36 h | 0.6 | 4 | 5–60 mg | 0.25 | 7.5 |
| Methylprednisolone | 12–36 h | – | 5 | 500–1000 mg | 0.2 | 6 |
| Dexamethasone | > 48 h | – | 30 | 2–24 mg | 0.04 | 1.5 |
| Budesonide | n.a. | n.a. | > 30 | 400–1600 mg | n.a. | n.a. |

multiple GR isoforms exist.[3] The GR contains DNA-binding and ligand-binding domains.[4] It binds to several other proteins including heat shock protein 90, which interacts with the ligand-binding domain and thereby maintains the receptor in an inactive state.[5] Activation of the GR requires binding of a ligand that results in GR hyperphosphorylation and translation into the nucleus. The transcriptional effects of the GR are mediated through interaction of its DNA-binding domain with glucocorticoid-responsive elements (GRE), which are specific DNA sequences. The transcriptional activity of the GR is conferred by additional coactivators that comprise a group of proteins inducing conformational changes in the GR, which in turn promote GR-mediated transcriptional activation.[6] Still, it has not been fully understood how a receptor such as the GR can mediate a variety of different effects on the cellular level. Ligand binding to the GR can result in a direct induction or repression of target gene expression. Furthermore, steroid-mediated induction of transcription factor expression controls numerous additional genes that contribute indirectly to the multitude of steroid-exerted effects.[7]

The clinical applications of synthetic steroids (eg, their use for the treatment of brain tumor edema or their antilymphoma activity) are frequently limited by their diminishing effect over time. The underlying mechanisms that preclude durable responses to steroids have been largely unknown. On the cellular level, the administration of drugs that act as agonists on the GR induces a downregulation of GR expression,[8,9] an effect mediated by reduced GR transcription, decreased half-life of GR mRNA, and reduced stability of the GR protein.[10,11] Together with other cellular processes, these mechanisms may contribute to the development of resistance to steroid treatment in different conditions. Steroids are finally metabolized in the liver in a cytochrome P450-dependent manner.[12] Combined administration of drugs that act as P450 inducers, such as the anticonvulsant phenytoin (which is still commonly used) may therefore alter the turnover of glucocorticoids and reduce their bioavailability.[13,14]

## Indications for the Use of Steroids

### *Antiedema Activity*

The striking antiedema effects of steroids were recognized several decades ago.[15] Since then, glucocorticoids have been used for various conditions in which a reduction of the intracranial pressure due to a peritumoral fluid collection must be achieved. Accordingly, steroids are commonly applied in a prophylactic manner perioperatively, during radiation therapy, and whenever rapid relief is required for clinical symptoms due to mass effect in the brain.[16,17] Steroids modulate the permeability of the blood-brain barrier, which is frequently compromised in brain tumors because both benign and malignant brain tumors secrete various cytokines such as vascular endothelial growth factor (VEGF) that act on endothelial cells located within or around the tumor. Although edema is most commonly found in patients with malignant lesions such as high-grade gliomas or metastases, it can also increase the mass effect of benign tumors such as meningiomas.[18,19] The effects of glucocorticoids on the blood-brain barrier are mediated through various genes and molecules, including claudins, occludin, zona occludens (ZO)-1, and vascular endothelial (VE)-cadherin, that influence endothelial permeability. Steroid administration decreases the permeability of the blood-brain barrier and limits the extravasation of fluid.[20,21] Similar to other steroid effects, the antiedema activity is temporary. Even in the context of scenarios with ongoing antiedema benefits, sustained administration of steroids can impair quality of life because of severe side effects (discussed below).

### *Treatment of Lymphomatous Neoplasms*

Primary CNS lymphomas (PCNSLs) or secondary lymphomatous neoplasms of the brain typically respond quickly upon administration of steroids that can induce cell cycle arrest and cell death, mostly apoptosis in a p38 mitogen-activated protein kinase (MAPK)-dependent manner, in B and T cells.[17,22,23] Accordingly, various treatment regimens for lymphomas comprise steroids, at least in the beginning of the treatment, when rapid effects are required. However, steroid effects against lymphomas are transient, and the tumor recurs in virtually all patients unless a chemotherapeutic regimen or irradiation is applied.[24] When a lymphoma is suspected, the administration of steroids should be avoided to allow for histopathological confirmation of the diagnosis. Still, even in patients who have already been exposed to steroids, the diagnosis may be established successfully.[25] Furthermore, rapid clinical and radiographic responses to steroid administration are not restricted to lymphomas but can also be observed in patients suffering from inflammatory conditions. The situation is different for tumor entities other than lymphomas. There is no clinical evidence that steroids inhibit the growth of gliomas or metastases in human patients. However, data from preclinical studies suggest that the proliferation of some glioma cells is reduced upon exposure to dexamethasone.[26] This is at

odds with other reports claiming that steroids have no effect or even stimulate the growth of glioma cells.[27,28] Furthermore, there are concerns, which are largely based on preclinical findings, that the administration of glucocorticoids renders tumor cells resistant to chemotherapy.[29–31] It remains to be determined whether steroid intake truly interferes with the efficacy of chemotherapy in human patients in vivo. However, because of this concern, steroid administration in cancer patients should always be critically evaluated.

### *Antiemetic Properties*

Cancer patients receiving systemic chemotherapy are frequently affected by severe nausea and vomiting. Chemotherapy-induced nausea and vomiting (CINV) can severely impair quality of life and induce further complications such as dehydration and electrolyte disturbances. Various drugs, including the widely used 5-$HT_3$ receptor antagonists and the neurokinin-1 receptor antagonist aprepitant, are available for the prophylaxis and treatment of CINV. Corticosteroids such as methylprednisolone and dexamethasone have also been used as antiemetic agents for decades.[32] Similar to other steroid-mediated effects, the receptors and pathways contributing to these effects have only been partially understood. Reduced release of 5-$HT_3$ from blood cells upon administration of steroids as well as direct effects on cellular 5-$HT_3$ receptor expression have been suggested as important factors.[33,34] Furthermore, preclinical data point to a direct effect of corticosteroids in the medulla oblongata.[35] Steroids are administered either alone or in combination with other drugs. The combination of a 5-$HT_3$ receptor antagonist, aprepitant, and dexamethasone has been recommended for prophylaxis in patients treated with moderately or highly emetogenic chemotherapy and are therefore at high risk for developing CINV.[36] Recent data from a randomized double-blind study indicated that dexamethasone and aprepitant have similar activity in preventing emesis in breast cancer patients receiving a chemotherapy regimen containing anthracyclines plus cyclophosphamide.[37] Furthermore, there was no significant difference in the toxicity profile of the 2 antiemetic regimens used in this trial. Accordingly, the value of steroids in the prophylaxis and treatment of CINV remains undisputed, and their use as single agents may be sufficient in some patients.

## Dosing and Tapering

The vast majority of patients suffering from brain tumors will receive steroids at some point in time during the course of their disease.[38] Although various synthetic glucocorticoids are available, dexamethasone is by far the most frequently used compound, most likely because of its properties described above.[39] In spite of the widespread use of glucocorticoids in brain cancer patients, there is hardly any evidence from clinical trials guiding the choice of dose, duration of treatment, and tapering schemes. A randomized trial assessed the activity of 8 mg dexamethasone versus 16 mg dexamethasone or 4 mg versus 16 mg in patients with brain metastases. A similar improvement of the Karnofsky performance status was observed in all groups. However, side effects were significantly more frequent in patients treated with 16 mg dexamethasone per day.[40] Whether the dose of glucocorticoids should be based on body weight or body surface area has not been examined either. Furthermore, it remains unclear whether elderly patients should receive lower doses than younger patients to reduce the risk of side effects and potentially lessen susceptibility to developing severely increased intracranial pressure. Finally, it remains doubtful whether doses higher than 16 mg dexamethasone per day provide additional beneficial effect.[41] Attempts to define a standard regimen for steroid application have largely failed, which means that the dose must be adapted to each patient's individual needs.[38] Not surprisingly, considerable variations have been observed in the administration and prescribing of steroids.[42] Because of steroid-associated toxicity, tapering should be considered as soon as clinically acceptable.[43] Although reliable data are lacking, it must be assumed that many patients receive steroids for too long and at a higher dose than necessary.[42,44] Steroids can be stopped quickly in patients who were taking them for a short period of time (ie, typically no longer than 10–14 days). In contrast, prolonged administration for weeks or months requires careful tapering over a longer period of time to avoid clinical deterioration because of manifest hypocortisolism due to suppression of adrenal function. To exclude the latter, basal cortisol levels in the morning may be determined at the end of tapering before the administration is stopped. Patients with insufficient cortisol levels can benefit from substitution with hydrocortisone, typically administered in 2 doses in the morning and at noon, to mimic the physiological secretion of the hormone. In the absence of particularly high cortisol needs, 20 mg in the morning and 10 mg at noon or early afternoon are sufficient for most patients.[45]

## Side Effects and Toxicity

Depending on the type and the dose of the administered steroid, side effects can occur in different ranges of severity. While some of these undesired effects only develop over time, others can manifest within days of the first steroid intake. Most of the symptoms are manageable; still, some side effects can be fatal when not recognized.

One of the most common side effects of steroid exposure is arterial hypertension, which occurs in at least 20% of patients treated with steroids in a dose-dependent manner.[46] This increase in systolic blood pressure is usually reversible, and cessation of steroid intake usually normalizes blood pressure again. If stopping medication is not an option in the context of the disease, symptomatic treatment of hypertension must be established, preferentially with diuretics, becauses hypervolemia induced by steroids is a main cause of hypertension in these patients.

Another relevant side effect of steroid use is the negative impact on the immune system, leading to a higher susceptibility to fungal infections such as candidiasis and *Pneumocystis jirovecii* pneumonia (PJP).[47] In high-risk patients with an impaired immune system, such as patients after organ transplantation or patients undergoing chemotherapy or radiotherapy, prophylactic treatment for PJP involving trimethoprim-sulfamethoxazole should be evaluated if prolonged steroid exposure is deemed necessary.[48]

Side effects that occur mainly in the long-term course of steroid exposure, but should be considered early to avoid morbidity, include osteoporosis and steroid-induced diabetes. Glucocorticoid-induced osteoporosis is the most common form of iatrogenic

osteoporosis and may occur in up to 50% of steroid-treated patients.[49,50] It involves an increased risk of fractures with more than a 5-fold increased risk of hip or vertebral fractures,[51,52] which are associated with increased morbidity and mortality. The use of bisphosphonates should be evaluated, and vitamin D and calcium should be supplemented at doses of 800 IU and 800–1200 mg per day in such patients.[53] In brain tumor patients requiring steroids and antiepileptic medication, caution needs to be taken because drugs such as valproic acid or phenytoin may also promote osteoporosis.[54–56] Replacing these agents with anticonvulsants having a more suitable toxicity profile should be considered.

Diabetes occurs in up to 50% of steroid-treated patients and is the most common form of drug-induced diabetes mellitus.[57] Accordingly, blood sugar levels should be determined regularly in patients taking steroids, especially when diabetes preexists. Management of steroid-induced diabetes does not differ from that of regular type 2 diabetes, and patients with repeatedly pathological blood sugar levels should be treated adequately to prevent long-term complications including cardiovascular and renal damage.

Steroid-induced myopathy has been described in up to 60% of patients taking steroids and is caused by decreased protein synthesis and induction of muscle protein catabolism.[58] Two distinct types of steroid-induced myopathy are described: the less common acute form, a generalized myopathy partially associated with rhabdomyolysis that occurs within days after the onset of steroid treatment and is often associated with high doses of steroids,[59,60] and the classic form, a chronic myopathy characterized by proximal muscle weakness that develops over a longer time course after prolonged steroid administration.[58,61] Myopathy may have even more devastating impacts on patients who already have a motor deficit or balance issues relating to their tumor. It has repeatedly been claimed that myopathy occurs more frequently when fluorinated steroids are administered.[62–64] However, compelling evidence from clinical trials comparing fluorinated and non-fluorinated steroids is lacking. Accordingly, due to its long half-life, low mineralocorticoid effects and high glucocorticoid potency, dexamethasone, a fluorinated drug, remains the first choice of steroid for brain tumor patients. Recovery from myopathy after dose reduction or tapering may take months, and physical therapy is recommended to attenuate the symptoms.[65]

Psychiatric effects of steroids have been described to occur in up to 60% of patients[66,67] throughout the treatment period. Early symptoms begin within 2 weeks and are most often dose dependent (eg, insomnia, emotional lability, hypomanic and manic episodes), whereas other symptoms may appear later in the course of treatment (eg, depression).[68,69] These symptoms tend to resolve after cessation of steroid treatment. During treatment with steroids, neuroleptic drugs (eg, olanzapine) may be required to ameliorate some of these behavioral sequelae. Finally, steroid intake is associated with an increase in cataracts and the rare occurrence of avascular bone (eg, hip) necrosis. A summary of the most relevant steroid-associated side effects, as well as potential prophylactic measures and therapies, is provided in Table 2.

## Steroids and Immunotherapy

Immunotherapy has gained increasing interest in neuro-oncology because of novel agents that are successfully used or currently being evaluated in late-stage clinical development in other tumor entities. The emergence of various immunotherapeutic approaches poses a particular challenge for the use of steroids because of their well-known immunosuppressive effects. Steroid-induced lymphopenia increases the risk for opportunistic infections (see above) but may also limit therapeutic approaches that aim to activate the immune system and boost antitumor immune responses.

One of these novel immunotherapeutic agents (eg, ipilimumab) targets cytotoxic T lymphocyte-associated antigen 4 and interferes with the inhibition of T cell function, which subsequently translates into enhanced antitumor activity. The drug has already been registered for the treatment of advanced melanoma,[70] and current efforts are defining its potential activity in patients with malignant gliomas. Similarly, targeting of the immune cell receptor programmed cell death (PD)-1 or its ligand PD-L1 is currently in advanced clinical development,[71] and clinical trials combining ipilimumab with the anti-PD-1 antibody nivolumab are currently ongoing for patients with glioblastoma.[72]

Another immunotherapeutic concept, vaccination, has also progressed within the last several years.[73] Again, steroids may interfere with boosting an immune response and therefore be counterproductive for patients who are being treated with a vaccine. Accordingly, several vaccination trials restrict the use of steroids at the time of enrollment to select only patients with a suitable immunological profile.

## Steroid-sparing Drugs

Because of the limited activity of steroids and, even more importantly, the side effects associated with their administration, steroid-sparing drugs may be very welcome. However, few viable alternatives are available. Bevacizumab, which is a VEGF-neutralizing antibody, has strong antiedema activity in the brain.[74] However, approval for this indication is lacking, and cost is presently a limiting factor. The administration of corticorelin acetate, a synthetic analog of human corticotropin-releasing factor, to brain tumor patients has allowed for a higher maximal reduction of the dexamethasone dose compared with control-treated patients in a randomized trial. Furthermore, patients in the corticorelin acetate group were less likely to be affected by myopathy and cushingoid appearance.[75] Drugs with uncertain effects on the edema surrounding brain tumors include boswellic acids, cyclooxygenase (COX)-2 inhibitors, and angiotensin-II inhibitors (reviewed in[76]).

## Conclusion and Outlook

The introduction of steroids 60 years ago was a milestone for the treatment of brain tumor patients. Their rapid effect on tumor-associated edema makes them indispensable even all these decades after their first administration, and steroids remain a mainstay in the management of brain tumors. Despite their widespread use, hardly any data from larger clinical studies exist, which preclude definite answers to important questions including the choice of the most appropriate synthetic drug, the most effective dose, and the optimal time-point for tapering. Chronic administration of steroids can be associated with severe side effects, which must be considered in any patient with regard to quality of life and functional autonomy. Steroid independence

**Table 2.** Steroid-associated side effects

| Side Effects | Frequency[a] | Symptoms | Prophylaxis/Treatment |
|---|---|---|---|
| Cushing's syndrome | | Moon face<br>Hyperglycemia<br>Hypertension<br>Striae | P: stay below Cushing threshold (see Table 1)<br><br>T: tapering steroid dose below Cushing threshold |
| Osteoporosis | Up to 50% | Pain<br>Fractures | P: short treatment periods<br>T: Calcium and Vitamin D supplement, bisphosphonates |
| Myopathy | Up to 60% | Muscle weakness | P: stay below 10 mg/d prednisone (equivalent)<br>T: switch from fluorinated to non-fluorinated steroids physical therapy |
| Steroid-induced diabetes | Up to 50% | Cardiovascular alterations<br>Renal failure<br>Visual impairment | P: regular blood sugar samples for early diagnosis<br><br><br>T: diabetes mellitus type 2 therapy regimen (including insulin if necessary) |
| Thrombembolic events | 3-fold increased compared to untreated[78,79] | Deep venous thrombosis<br>Pulmonary embolism<br>Stroke | P: compression hosiery, low-dose heparin, mobilization<br><br>T: oral anticoagulants or heparin in therapeutic doses |
| Immunosuppression | 30%–100% | Opportunistic infections<br>Wound healing problems<br>Ulcerations | P: regular white blood count<br>T: prophylactic or therapeutic trimethoprim-sulfamethoxazole<br><br>Antibiotics<br>Antacids |
| Psychiatric disorders | Up to 60% | Insomnia<br>Mood disorders<br>Psychosis | P: stay below 40 mg/d prednisone (equivalent)<br><br>T: neuroleptics, sedatives |

Legend to Table 2: P, prophylaxis; T, therapy.
[a]upon prolonged use.

should be incorporated as exploratory endpoints in future trials in brain tumor patients, as has already been done in the AVAGLIO trial.[77] A better understanding of the cellular mechanisms mediating the clinical activity of corticosteroids may help to design novel compounds that selectively confer the urgently needed beneficial effects but are no longer associated with detrimental toxicity. In parallel, intense research is needed to find novel strategies that allow other compounds to substitute for steroids. The ongoing development and clinical assessment of corticorelin acetate could be a first step towards a reduction of steroids doses and associated side effects. However, a final evaluation of this drug is pending, and data from additional trials need to be awaited.

## Funding

No funding was obtained for the preparation of this manuscript

*Conflict of interest statement*. PR has received honoraria for advisory boards from Roche, MSD, and Molecular Partners. CH has received honoraria for advisory board activity for MSD. MW has received research grants from Bayer, Isarna, Merck Serono, MSD, and Roche and honoraria for lectures or advisory boards from Isarna, Magforce, Merck Serono, MSD, and Roche.

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