



## Pharmacology Update

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# Dexamethasone Therapy in Patients with Brain Tumors— A Focus on Tapering

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Corticosteroids, a class of agents similar to natural corticosteroid hormones produced by the adrenal gland, are routinely prescribed for patients with brain tumors. These agents decrease tissue swelling and control signs and symptoms of brain tumors, including headaches, seizures, motor deficits, and altered mental status. Synthesized in the adrenal cortex, corticosteroids may be further divided into two classes, glucocorticoids and mineralocorticoids, based on their biologic activity.

Originally, the term *glucocorticoid* was given to agents such as hydrocortisone and prednisone to describe their effects on carbohydrate and protein metabolism, and the term *mineralocorticoid* was given to aldosterone and fludrocortisone and described their effects on regulating electrolyte and water homeostasis. However, carbohydrate metabolism is only one

of a multitude of effects that glucocorticoids produce within the body, and the activity produced is a function of the specific receptor activated (i.e., glucocorticoid versus mineralocorticoid), as well as the agent and the prescribed dose (Gans & Smith, 1999).

This article provides an overview of the mechanism of action of corticosteroids and rationale for their use in patients with brain tumors. Practical implications on dosing, tapering, and side effects of dexamethasone are discussed as well.

### Mechanism of Action

Glucocorticoid receptors are found intracellularly in almost all tissues. Glucocorticoids enter cells through passive diffusion and form a complex with a receptor protein. This complex then undergoes an irreversible activation and enters the cell nucleus, where it binds to DNA, leading to biological effects induced by these hormones, including increased hepatic gluconeogenesis, increased lipolysis, muscle catabolism, and inhibition of peripheral glucose uptake in muscle and adipose tissue (Gans & Smith, 1999; Greenspan & Stewler, 1997). The exact mechanism of action of corticosteroids remains unknown despite more than 40 years of research.

### Rationale for Use

Corticosteroids decrease brain edema. In central nervous system tumors, corticosteroids have been found not only to reduce peritumoral and vasogenic brain edema, but also reduce increased intracranial pressure and frequency of plateau waves,

decrease cerebral spinal fluid production, and decrease tumor cerebral blood flow (Behrens, Ostertag, & Warnke, 1998; Koehler, 1995; van Roost, Hartmann, & Quade, 2001). The primary corticosteroid used to control cerebral edema is dexamethasone. More than 40 years ago, dexamethasone was used in patients with brain tumors, and it is still used today. Other steroids at equivalent doses probably also work, but given the clinical ease of use and comfort, dexamethasone is used.

Although corticosteroids decrease capillary permeability in the tumor itself, it has been found in animal models that dexamethasone may act differently and decrease edema by effects on bulk flow away from the tumor (Molnar, Lapin, & Goothuis, 1995). In addition, corticosteroids also improve patients' level of alertness and reduce or eliminate focal deficits (Anderson, Astrup, & Gyldensted, 1994; DeAngelis, 1994; Fishman, 2000).

Additional support for corticosteroid therapy in neurosurgical patients includes high concentrations of glucocorticoid receptors in certain types of brain tumors (Yu et al., 1981). Tumors that respond well to dexamethasone, such as cerebral metastases, are characterized by high levels of glucocorticoid receptors. Tumors known to respond less favorably, such as meningiomas, are characterized by lower levels of glucocorticoid receptors. In addition, the level of edema associated with a meningioma is dependent on various factors including size, location, malignant grade, and most importantly,

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secretion of vascular endothelial growth/permeability factor. Dexamethasone has been found to impede this factor in cultured cells (Criscuolo & Balledux, 1996).

As a result of these actions and the initial work of early investigators (French & Galicich, 1964), glucocorticoids, specifically dexamethasone, are now routinely administered to brain tumor patients. Dexamethasone has been the corticosteroid of choice in this patient population because of its high potency relative to other agents, its low mineralocorticoid (sodium retaining) effect, and its long biologic half-life (i.e., 48 hours). Dexamethasone is initially dosed every 6 hours but it need not be because of long half-life and could be dosed every other day.

### Dosage

The usual but empirical initial dose in brain tumor patients is an intravenous bolus of 10 mg of dexamethasone, followed by a maintenance dose of 4 mg given by the intravenous (IV) route every 6 hours (16 mg/day) (Szabo & Winkler, 1995). Because of both rapid and complete absorption from the gastrointestinal tract, dosing of oral and parenteral glucocorticoids is equivalent, and intravenous therapy should be converted to oral therapy at the earliest appropriate opportunity. Higher daily dexamethasone doses can be given to patients who do not respond to the usual initial dose. Response is usually measured in terms of improvement in neurological deficits within 48 hours. Corticosteroids can produce an improvement in neurologic symptoms and reduction in cerebral edema within the first 8 to 48 hours, with 12 to 24 hours being the usual time frame.

In recent years, doses as high as 100 mg per day of dexamethasone have been used occasionally in situations of imminent herniation or to achieve rapid stabilization prior to urgent surgery (DeAngelis, 1994). Preoperatively, doses may be increased to 40 mg but often a change in dosing is not warranted. Intra-

operative dosing is not usually relevant to brain tumor patients, because intracranial pressure adjustment is managed by the anesthesiologist with various other drugs including IV fluids, pressors, and mechanical ventilation. Postoperatively, decisions regarding dosing are influenced by the type of brain tumor and extent of surgical resection, length of surgery, and other intraoperative complications, but often the standard dosing protocol of 4 mg IV every 6 hours is ordered.

### Dexamethasone Tapering

Corticosteroid therapy must be tapered because of its interactions with the hypothalamic-pituitary-adrenocortical (HPA) axis. The hypothalamus secretes corticotropin releasing factor, which acts on the anterior pituitary, where it stimulates the secretion of adrenocorticotropin (ACTH). The adrenal glands are stimulated by ACTH to release approximately 20 mg of cortisol per day, with peak levels occurring in the morning. Through a negative feedback mechanism, an increase in circulating cortisol results in the inhibition of this cycle and suppression of its activity. Suppression of the HPA axis affects a patient's ability to respond to an acute stressful event and chronically causes the axis to atrophy.

Typical doses of dexamethasone used in the brain tumor patient are pharmacologic (i.e., supraphysiologic) in nature and have the potential to suppress the HPA axis if given over a prolonged period of time (e.g., more than 2 weeks), or are abruptly tapered or withdrawn. Dexamethasone provided 4 mg at every 6 hours, the usual initial dose—equivalent to 400 mg of cortisol per day—is about 20 times the normal rate of endogenous production. In patients who have received less than 14 days of dexamethasone therapy, treatment may be abruptly discontinued without adverse events, because the HPA axis is not suppressed (Kountz & Clark, 1997; Szabo & Winkler, 1995). However, some rebound edema may occur and symptoms may recur abruptly.

In clinical practice, dexamethasone tapering schedules are often prescribed for short-term therapy, and usually consists of an empiric reduction in dose of 2–4 mg every 1–3 days, by either reducing the dose and/or the interval. Other tapering schedules have been reported in this patient population and include a “slow taper” of lowering the dose by 4 mg every week. In reality, the dose of dexamethasone and tapering schedule should be adjusted to the patient's tolerance.

Dexamethasone is often used during radiation therapy (RT). Higher doses are used at the onset of and during RT with lower doses at the end of RT (Hempfen, Weiss, & Hess, 2002). Research has shown that twice daily dosing of dexamethasone can provide a good clinical response with minimal morbidity (Weissman, et al., 1991). Dosages should be adapted to each individual patient's needs, because some patients can experience radiation side effects or neurological symptoms without dexamethasone (Hempfen, Weiss, & Hess).

Often corticosteroid therapy continues beyond 14–21 days to control symptoms of brain tumors, and gradual reductions in dosing must occur. The concept of a tapering schedule for chronic corticosteroid therapy evolved to prevent adrenal insufficiency syndrome and recurrence or exacerbation of signs and symptom. Patients are more likely to adhere to medication schedules if signs and symptoms are controlled and tolerated.

Although algorithms have been developed and utilized to assist clinicians in safely withdrawing patients from chronic corticosteroid therapy (Kountz & Clark, 1997), tapering schedules remain, at best, empiric and dependent on patient specific responses. A gradual decrease in dose and/or dosing interval of dexamethasone every 3–7 days, in an attempt to reach a physiologic dose equivalent to 20 mg of cortisol per day (i.e., approximately 0.75 mg of dexamethasone per day), should be attempted (Szabo & Winkler, 1995).

Cortisol levels peak in the morning, so a once per day or every other day morning dose of corticosteroid is optimal to minimize suppression of the HPA axis. It is suggested that after the patient is tapered to a dose of 0.75 mg of dexamethasone per day, a morning cortisol level should be drawn to determine the steroid's effect on adrenal function. If the cortisol level is greater than 10 mcg/dl, the steroid therapy can be stopped. If the morning cortisol level is less than 10 mcg/dl, the adrenal glands are still suppressed and the steroid taper should continue over 4 more weeks (Szabo & Winkler, 1995).

If further steroid tapering is required, the patient should then be switched to a more intermediate acting steroid, such as prednisone, because long-acting corticosteroids like dexamethasone do not provide a steroid free period for recovery from adrenal suppression, and prednisone also allows for more flexible dosage adjustments (Spruill & Wade, 1988). After 4 weeks, another cortisol level should be drawn. After the level is greater than 10 mcg/dl, steroid therapy may be discontinued.

To verify HPA axis recovery, the rapid ACTH stimulation test may also be utilized. A synthetic analog of ACTH, cosyntropin 0.25 mg is administered by the IV or intramuscular route. Cortisol levels are drawn before the dose is administered and again 30 min. after administration. If the increase in cortisol is less than 6 mcg/dl, the HPA axis is still suppressed and the patient still requires supplementation for another 4 weeks. If the increase is greater than 6 mcg/dl, the patient no longer requires steroid therapy, because adrenal function has returned to normal (Szabo & Winkler, 1995).

Patients receiving chronic glucocorticoid therapy may require up to 12 months for all components of the HPA axis to recover full function and are recommended to wear a Medic-alert bracelet, in the event that they are exposed to a stressful event and may not be able to mount an effective adrenal response (Kountz & Clark, 1997). Evidence of an effective adrenal response include lack of cortisol defi-

ciency without weakness and fatigue, anorexia, nausea and vomiting, hypotension, hypoglycemia, hyponatremia, and increased susceptibility to infection (Greenspan & Stewler, 1997).

### Adverse Effects

The myriad of adverse effects from corticosteroid therapy are well known to physicians, nurses, pharmacists, and patients. In general, adverse effects are dose- and time-dependent with 50% of patients experiencing at least one toxicity symptom. Commonly encountered adverse effects include hyperglycemia, gastritis, gastrointestinal bleeding, weight gain and moon faces, osteoporosis with chronic therapy, psychosis or euphoria, immunosuppression causing increased susceptibility to infection, and skin fragility and striae (DeAngelis, 1994; Vecht et al., 1994). In addition, steroid myopathy can occur, causing weakness primarily to proximal muscles of the upper and lower extremities and neck, which is frequently confused with progressive neurological disease.

Nurses may need to educate patients on management of blood sugar levels including possible use of insulin. To prevent gastrointestinal complications, encourage patients to take steroids with food and avoid aspirin and nonsteroidal anti-inflammatory drugs. Neuroscience nurses often confront body image disturbances of patients who experience weight gain and a "moon face" as a result of steroid use, requiring emotional support and counseling in dietary modifications such as low calorie snacks. Reassure patients that weight gain will not usually continue when dexamethasone is tapered off.

Musculoskeletal effects can be potentially disabling, so patients should be encouraged to exercise, if possible. Infection control measures include avoidance exposure to cold- and flu-like symptoms in others. Nurses will often need to assess patients' oral cavities for candida infection. If insomnia is a problem, sleep aids and avoidance of daytime napping may help. Both patients and family members should be

alerted to possible personality changes that may occur with dexamethasone use. Family members need to be included in education efforts, because they are often the individuals who note patient responses to treatment and changes in behavior.

Although most of these adverse effects occur with chronic corticosteroid therapy, patients often experience some of these with short-term therapy. The highest incidence of toxicity was evident in patients with serum albumin levels below 2.5mg/dl (Weissman, Dufer, Vogel, & Abeloff 1987). Because corticosteroids are highly bound to serum albumin, a decrease in the serum albumin level will result in a higher concentration of unbound corticosteroid in the circulation, thus increasing the potential for toxicity. Fortunately, serum albumin levels are usually not a problem in brain tumor patients.

Dose tapering can exacerbate pre-existing conditions such as pain, arthritis, asthma, dental conditions, and drug rash because of an antiepileptic drug. The treatment for an antiepileptic drug rash is to stop the drug; rarely are antihistamines or steroid creams ordered. The hepatic clearance of most antiepileptic medications is affected by steroids, necessitating careful monitoring of antiepileptic drug levels. Corticosteroids also decrease the effectiveness of oral contraceptives, therefore, dose adjustments and sexual counseling are needed in relevant patients. Thromboembolic risk may also increase in a patient population already at high risk for venous thrombosis.

Preventive measures can be initiated to avoid some of the more common adverse effects. Dietary counseling for optimizing nutritional status with a diet high in protein (to maintain an adequate serum albumin), vitamins, and micronutrients are recommended for the patient requiring chronic corticosteroid therapy. In addition, nutritional counseling can guide the patient in the selection of low-calorie and low-fat snacks for those who experience an increase in appetite and weight gain. Doses of corticosteroids may be taken with food. An antacid, or an H-2

antagonist or proton pump inhibitor may be added to the patient's medication regimen to reduce the incidence of gastritis and gastrointestinal bleeding.

Calcium and vitamin D supplementation can also be prescribed to reduce the loss of bone mass associated with long-term use of steroids. In addition, alendronate (Fosamax) and risedronate (Actonel) are prescribed to prevent steroid-induced osteoporosis and subsequent fractures. To date, risedronate is the only medication approved by the Food and Drug Administration for this use.

## Drug Interactions

Phenytoin, an antiepileptic medication frequently prescribed for seizure prophylaxis in patients following neurosurgery, has been shown to decrease the serum half-life of dexamethasone by increasing its metabolism. This interaction may account for the variations in the optimal dexamethasone dose in a large number of brain tumor patients receiving prophylactic antiepileptic medications. Phenobarbital, another antiepileptic medication, has also demonstrated a similar effect on dexamethasone. Both of these agents are potent inducers of the hepatic microsomal enzyme system, which would explain their effect on dexamethasone metabolism. Hence, newer anti-epileptic drugs with no hepatic enzyme inhibition, such as gabapentin and levetiracetam, may be preferable for patients who need seizure prophylaxis. The interaction of dexamethasone and other anti-epileptic drugs has not been well studied. Careful monitoring and dose adjustments may be required to achieve therapeutic drug concentrations (Gattis & May, 1996).

## Summary

Administration of corticosteroids in brain tumor patients requires an understanding of the physiology of the adrenal system and desired patient response. Close attention to other concomitant medications will ensure adequate amounts of all drugs, including dexamethasone. Nurses need to assess patients' tolerance of dexamethasone,

discuss these findings with physicians and pharmacists, and educate both patients and family members on doses and tapering schedules tailored to individual patient needs.

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