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GLUCOCORTICOIDS IN VETERINARY NEUROLOGY / NEUROSURGERY: THE GOOD, THE BAD AND THE UGLY

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PATHOPHYSIOLOGY OF CORTICOSTEROIDS

Pharmacological correlates of the endogenous glucocorticoids are used frequently in companion animals for their anti-inflammatory and immunosuppressive effects. However, these properties are not selective, and corticosteroids will affect many body systems beyond the "target tissue," potentially causing adverse effects. The most critical goal in using glucocorticoids is to achieve a balance between control of disease and the induction of adverse effects.

Adverse effects, which are less common in cats than in dogs, include the following:

1. Adrenal atrophy. Slowly reversible after cessation of glucocorticoid therapy. However, hypoadrenocorticism may occur if glucocorticoids are withdrawn suddenly.
2. Excess gluconeogenic, protein catabolic and lipolytic effects. May lead to hepatomegaly (steroid hepatopathy) and hyperglycemia, with polyuria/polydypsia/polyphagia and weight gain.
3. Cats are particularly susceptible to the hyperglycemic effects of glococorticoids (stress hyperglycemia).
4. Dogs are particularly susceptible to steroid induced polyuria/polydypsia at anti-inflammatory doses.
5. Induction of alkaline phosphatase in dogs (but not cats). This does not appear to have a pathological consequence.
6. Long-term administration of corticosteroids has been shown to induce proteinuria and glomerular pathology in dogs.
7. Suppression of immune and inflammatory systems may result in increased susceptibility to secondary infection (e.g., urinary tract infection), or may potentiate viremia (e.g., in cats that are carriers of calicivirus or feline herpes virus).
8. Hypertension.
9. Gastric ulceration and hemorrhage (most frequent when a concurrent "ulcerogenic" stimulus is present such as NSAID administration).
10. Pancreatitis.
11. Behavioral changes.

As with all drugs, corticosteroids have an optimal dose for either anti-inflammatory or immunosuppressive effects in different target organs. Despite the widespread use of corticosteroids, there is no consensus in the veterinary literature regarding the optimal form, dose, route or duration of corticosteroid therapy for different conditions.

CLINICAL APPLICATIONS IN VETERINARY NEUROLOGY AND NEUROSURGERY

Clinical indications for glucocorticoids include the treatment of inflammatory, immune-mediated (autoimmune) or neoplastic (e.g., lymphoma, mast cell tumor) diseases of the nervous system.

"THE GOOD"

This group of diseases includes numerous disorders of the nervous system in which the use of glucocorticoids appears to be indicated. While the optimal form, dose, route or duration of corticosteroid therapy for the different conditions in this group have not been elucidated, there is considerable anecdotal information that supports the use of a variety of anti-inflammatory or immunosuppressive approaches.

Neoplasia. Anti-inflammatory doses of glucocorticoids provide the basis for the palliative management of brain and spinal cord neoplasms. The anti-inflammatory and anti-edema effects of corticosteroids may result in resolution of clinical signs for significant periods of time. Glucocorticoids also may have a direct effect in reducing the size of some central nervous system tumors (e.g., lymphoma).

Steroid Responsive Meningitis-Arteritis. Prognosis is guarded to favorable in dogs that are treated promptly using immunosuppressive doses of glucocorticoids. Untreated dogs are likely to have a remitting and relapsing course.

Granulomatous Meningoencephalomyelitis (GME). Prognosis for permanent recovery is poor. Long term therapy generally is unsatisfactory, although temporary remission of signs may be achieved with corticosteroid administration (oral prednisone 1-2 mg/kg/day initially for several days, then reducing the dosage to 2.5-5 mg on alternate days). Most dogs require continued therapy to prevent recurrence of signs. Improvement may last for weeks or months, although almost all dogs will die from the disease. Part of the temporary improvement may be related to a reduction of mast cell function in dogs receiving glucocorticoids. Cessation of glucocorticoids frequently results in rapid deterioration. Recently, procarbazine or cytosine arabinoside have been successful as sole long-term treatments for GME.

Corticosteroids are indicated for several immune-mediated neuromuscular diseases (e.g., masticatory muscle myopathy and polymyositis)

"THE BAD"

This group includes disorders in which the use of glucocorticoids may be indicated in specific circumstances, with careful selection of the optimal form, dose, route of administration, and duration of corticosteroid therapy.

Spinal Cord Trauma. Considerable controversy exists concerning the most appropriate management methods for acute spinal cord injury in dogs and cats. Experimental and clinical investigations to date suggest

that the functional outcome following spinal cord injury in humans, rats and cats may be influenced by management of systemic blood pressure and by use of methylprednisolone sodium succinate (MPSS) administered within 8 hours of an acute spinal cord injury. Currently, evidence does not exist to support the use of MPSS in dogs with acute spinal cord injury.

Intervertebral Disc Disease. Use of corticosteroids in the treatment of mild to moderate Hansen type 1 intervertebral disc disease is widespread in veterinary practice. The benefits of corticosteroid therapy for this purpose are anecdotal and unproven. Dogs with Hansen type 2 intervertebral disc disease may show improvement of neurological status following anti-inflammatory doses of glucocorticoids. While this also is anecdotal, it appears that such treatment may be effective for many months. However the underlying disease process has not been addressed, and progression of clinical signs ultimately will occur.

Infectious CNS Disease. While the immunosuppressive effects of glucocorticoids may appear to be contraindicated in the face of infectious diseases affecting the nervous system, anti-inflammatory doses of corticosteroids have been recommended for short periods at low doses when neurological signs are severe. However, recent evidence suggests that glucocorticoids are not always anti-inflammatory, and may even be "pro-inflammatory" in central nervous system inflammation.

Myasthenia Gravis. Dogs and cats that do not respond well to anticholinesterase treatment may be considered candidates for corticosteroid therapy. In fact, in cats where tolerance of corticosteroids is much better than that of dogs, this approach has been recommended as a first line treatment. Glucocorticoids at immunosuppressive doses should be administered with caution to myasthenic animals, as they may lead to an exacerbation of weakness, the mechanism for which has been poorly defined. Myasthenic dogs should initially be given glucocorticoids at anti-inflammatory doses, which may be increased to immunosuppressive levels over a 1-2 week period.

"THE UGLY"

This group includes those situations and disorders where use of corticosteroids is contraindicated. This situation often is compounded by poor choices with regard to optimal form, dose, route of administration, and duration of corticosteroid therapy.

Spinal Cord Trauma. Little support exists for the administration of dexamethasone for the treatment of acute spinal cord injury, and this practice is discouraged in the context of the high frequency of adverse gastrointestinal effects associated with this drug (e.g., colonic perforation), and its potential detrimental effects on the recovering nervous tissue. Further, the initiation of MPSS treatment more than 8 hours after injury may result in a worse outcome. The proposed mechanism for this finding is that glucocorticoids interfere with normal regeneration, and will enhance neurodegeneration by inhibiting neuronal glucose uptake in the face of ischemia and glutamate-induced damage.

Brain Trauma. Corticosteroids are not specifically indicated for the treatment of acute head trauma in people. The blinded Corticosteroid Randomisation After Significant Head injury (CRASH) trial completed in 2004 examined the effect of corticosteroid administration in the setting of traumatic brain injury. More than 10,000 patients were enrolled at 239 hospitals in 49 countries. Inclusion criteria were age 16 or older, Glasgow Coma Score 14 or less, and enrollment within 8 hours of injury. Participants were randomized to either a loading dose of 2 g of methylprednisolone by infusion followed by a dosage of 0.4 g per hour for 48 hours, or matching placebo infusion. The primary outcome measure for this report was death at 2 weeks (6-month outcomes are to be reported later). Compared with the placebo group, the risk for death was higher in the corticosteroid group (1052 [21.1%] vs. 893 [17.9%] deaths; relative risk, 1.18; 95% confidence interval, 1.09-1.27; *P*=0.0001). This relative increase in deaths did not seem to differ even when injury severity was taken into account (*P*=0.22). The participating clinicians were not asked to judge the causes of death. It seems that in human medicine, a routine treatment for patients with head injuries, widely used around the world for the last 30 years, does not improve survival rates and may do more harm than good. The findings of this large, well-designed study establish without question that steroid administration at the dosage studied is not beneficial and is probably harmful. However, there is a major qualification: only a single total dose was tested, and it was high (equivalent to that used in spinal cord injury studies). Given that the causes of death were not reported, the high dose may have caused complications such as gastrointestinal bleeding. Certainly, the reported clinical steroid regimens for head injury are highly variable, but most advocates recommend doses that are substantially lower than those used in this study. The effect at lower doses is unknown.

NSAIDs and Corticosteroids. NSAIDs should not be administered with corticosteroids or other NSAIDs.

CONCLUSION

When studying glucocorticoids and inflammation of the central nervous system, it is imperative to consider that effects will differ depending on many factors: type of glucocorticoid (e.g., endogenous or synthetic), glucocorticoid concentrations, location (e.g., CNS or periphery), type of inflammation, and immune cells involved (e.g., T cells, B cells, granulocytes). Considering these complex multifactorial interactions, and the increasing number of studies showing pro-inflammatory glucocorticoid effects, it seems appropriate to reconsider the dogma of glucocorticoids being universally immunosuppressive, and, the broad use of glucocorticoids as the anti-inflammatory drug of choice in a very large number of CNS disorders.

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