Corticosteroids have been used for decades in human and veterinary emergency and critical care medicine. There are two major groups of corticosteroids used to treat acutely and critically ill small animals: mineralocorticoids and glucocorticoids. Mineralocorticoids exert aldosterone-like effects on the kidney, increasing sodium reabsorption and potassium excretion in the distal nephron. They are used in veterinary medicine exclusively to treat patients with Addison’s Disease. Full discussion of this group of steroids is outside the scope of these proceedings. Glucocorticoids are drugs such as hydrocortisone, prednisone and prednisolone, methylprednisolone, and dexamethasone. Some of these drugs (particularly hydrocortisone) possess some mineralocorticoid activity, and they differ in their glucocorticoid effects and their durations of biologic action.

GLUCOCORTICOIDS

The major endogenous glucocorticoid is cortisol, a steroid hormone made from cholesterol in the adrenal cortex. Cortisol is released in small amounts in a circadian rhythm, and in larger amounts during times of physiologic stress, such as illness, trauma, or surgery. Glucocorticoid receptors are present in the cytosol of almost every cell in the body; thus, the hormone has numerous known, and likely many unknown, physiologic effects. Cortisol has many important homeostatic functions including regulation of carbohydrate, lipid, and protein metabolism; immune system modulation; ensuring proper production of catecholamines; and optimizing catecholamine receptor function.1,2

Pharmacologically, glucocorticoids are most commonly used for their modulatory effects on the inflammatory and immune systems. They inhibit cytokine production and neutrophil and macrophage activity, and also inhibit cellular immunity (T cell activity).1 They are also used to replace glucocorticoid that is deficient in patients with classic hypoadrenocorticism (Addison’s Disease); atypical hypoadrenocorticism (glucocorticoid-only hypoadrenocorticism); iatrogenic hypoadrenocorticism; and critical illness-related corticosteroid insufficiency. A few other conditions for which glucocorticoid therapy is indicated are discussed below.

All glucocorticoid drugs are structurally similar, though important differences in molecular structure significantly affect the mineralocorticoid activity, anti-inflammatory (glucocorticoid) potency, and duration of biologic action, which because their effects are genomic, are longer than their plasma half-life. In general, glucocorticoids that are not significantly structurally altered from the endogenous cortisol molecule (i.e., Cortisone, Hydrocortisone) have relatively more mineralocorticoid activity, less significant anti-inflammatory activity, and a relatively short duration of biologic action (< 12 hours). Conversely, drugs that are more structurally altered (i.e., Dexamethasone) have no mineralocorticoid activity, significant anti-inflammatory activity, and a long duration of biologic action (> 48 hours). Drugs with intermediate structural alteration (i.e., Prednisone, Prednisolone, and Methylprednisolone) have intermediate properties and duration of biologic activity (12 – 36 hours).2 Below is a short description of each of the drugs commonly used in the small animal emergency and critical care setting.

Hydrocortisone and Cortisone: Hydrocortisone is structurally identical to endogenous cortisol, and is biologically active as administered. Cortisone is inactive until it is converted by the liver to hydrocortisone. When administered systemically, cortisone is very similar to hydrocortisone, though with slightly less anti-inflammatory effect. Because cortisone requires hepatic conversion to hydrocortisone to be biologically active, cortisone is inappropriate for local or topical use. Both hydrocortisone and cortisone have a rapid onset of action and a relatively short duration of biologic action (< 12 hours), and both are available in oral and injectable preparations. Hydrocortisone sodium
succinate is probably the most commonly used of these preparations in the hospitalized animal. It is ideal for use in Addisonian patients in acute crisis, during illness, or undergoing anesthesia or surgery, as it is structurally identical to endogenous cortisol and has some mineralocorticoid activity. Injectable hydrocortisone is also the drug of choice for treatment of critical illness-related corticosteroid insufficiency (CIRCI - see below).³

**Prednisolone, Prednisone, and Methylprednisolone:** Prednisolone and prednisone have moderate structural alteration, so have little mineralocorticoid activity, good anti-inflammatory activity, and a moderate duration of biologic action (12 – 36 hours). These drugs have approximately 5x the anti-inflammatory potency of hydrocortisone. Prednisolone is biologically active as administered, but prednisone must be hepatically converted to prednisolone to become active. Therefore, prednisolone has topical or local applications, whereas prednisone does not. Once systemically absorbed and converted to prednisolone, prednisone is very similar to prednisolone, though with slightly less potent anti-inflammatory effects. Prednisone is commonly available for oral administration, whereas prednisolone is available in oral, injectable, topical ophthalmic, and other preparations. All common preparations (prednisone, prednisolone, prednisolone sodium succinate) have rapid onset of action. Both prednisone and prednisolone are commonly used in the emergency and critical care setting. Methylprednisolone is very similar to prednisolone, except that it has no mineralocorticoid activity; it is available in oral, injectable, and topical preparations.

**Dexamethasone:** Dexamethasone and other similar drugs (i.e., betamethasone) are significantly structurally altered such that they have no mineralocorticoid activity, very potent anti-inflammatory activity, and a long duration of biologic action (> 48 hours). Dexamethasone is biologically active as administered, and has approximately 7 – 10x the anti-inflammatory potency as prednisone, about 30x the potency of hydrocortisone. The most commonly used preparations (dexamethasone, dexamethasone sodium phosphate) have rapid onset of action (minutes to hours). Dexamethasone is commonly used in the emergency and critical care setting.

**Fluticasone:** Fluticasone (Flovent®, GlaxoSmithKline) is a highly structurally altered glucocorticoid intended for inhalation. It is used to treat asthma in humans and feline asthma in cats. Inhaled fluticasone has fewer systemic side effects than systemically administered glucocorticoids because of the drug’s large molecular size and its local administration. Fluticasone comes in a metered dose inhaler, which must be adapted using a species-specific spacer such as the AeroKat® (Trudell Medical International). Administration requires a calm and compliant patient, and the drug has an onset of action of one or more days. Therefore, fluticasone is not ideal for management of the unstable feline asthmatic; injectable steroids are probably easier and definitely have more rapid effects.

**INDICATIONS FOR GLUCOCORTICOID USE**

Glucocorticoids are some of the most commonly used and misused drugs in veterinary medicine. The most common indication is for treatment of immune-mediated and inflammatory diseases, management of specific hematopoietic neoplasias, and for replacement in animals with poor endogenous cortisol production. Glucocorticoids are also used in a few other specific situations, such as to treat hypercalcemia and to support blood glucose concentration in patients with insulinoma.

**Hypoadrenocorticism:** Appropriate fluid resuscitation and directed therapy for hyperkalemia and its cardiac consequences are by far the most important aspects of acute management in the Addisonian crisis. After the initial stabilization period, mineralocorticoid medication (see above) is indicated. Desoxycorticosterone pivalate (DOCP) may be administered after completion of the ACTH stimulation test. Alternately, fludrocortisone or hydrocortisone can be administered, though hydrocortisone’s mineralocorticoid activity may be inadequate if the patient is still in crisis. Patients in hypoadrenal crisis
should be treated with glucocorticoids. Recommended doses for hypoadrenal crisis are: dexamethasone or dexamethasone sodium phosphate 0.1 mg/kg IV initially followed by 0.05 mg/kg IV every 12 hours; prednisolone sodium succinate or methylprednisolone sodium succinate 1 – 2 mg/kg IV initially followed by 0.5 – 1 mg/kg IV every 8 – 12 hours; or hydrocortisone sodium succinate 1.25 mg/kg IV initially followed by 0.5 – 1 mg/kg IV every 6 hours. These doses should be tapered for maintenance once the animal is stable and eating.

**Immune-mediated disease of the hematopoietic system:** Steroids are the mainstay of therapy for immune-mediated cytopenias in dogs and cats because of their inhibitory effects on cellular immunity. Initial doses for the patient in an acute crisis are: dexamethasone or dexamethasone sodium phosphate 0.2 – 0.5 mg/kg IV daily (at once or divided); or prednisone or prednisolone sodium succinate 1.1 – 3.3 mg/kg IV every twelve hours. Some people anecdotally report better success with dexamethasone during an acute hemolytic or thrombocytopenic crisis. If the animal is going to respond to treatment, improvement is usually seen within 7 days, but response can take up to 4 weeks. Initial doses should be continued until red cell or platelet numbers increase substantially, and probably should not be tapered sooner than 2 weeks after induction. Further information is available in references listed below.

**Immunosuppression for transplant recipients:** Renal transplant recipients are managed in some small animal intensive care units. Recipients live across North America, and local primary and emergency caregivers may need to manage acute crises. Prednisolone is a mainstay of immunosuppressive therapy in cats and dogs undergoing renal transplantation. Feline renal transplant patients are treated initially and life-long with ~2.5 – 5mg prednisolone twice daily. Canine transplant patients are often treated initially with 0.5 mg/kg prednisolone every twelve hours, tapered over 3 months, and discontinued, though some are continued on life-long therapy. Some dogs and cats are weaned off prednisolone therapy if complications arise secondary to the drug (infections; diabetes mellitus in cats). Rejection of the grafted kidney usually requires short-term, increased doses of injectable glucocorticoid; however, graft rejection appears to be uncommon in dogs and cats, and no defined protocol is available in the literature.

**Other sterile immune-mediated or inflammatory disease:** Glucocorticoid therapy is a mainstay of treatment for sterile immune-mediated and inflammatory diseases in dogs and cats. Conditions seen in an emergency room or intensive care unit include: feline asthma; canine allergic bronchitis; eosinophilic bronchopneumopathy (pulmonary infiltrates with eosinophils); steroid-responsive meningitis of young, large-breed dogs; meningoencephalitis of unknown etiology (granulomatous meningoencephalitis); non-infectious, inflammatory or immune-mediated hepatitis or cholangitis; and immune-mediated dermatopathies. Most of these conditions require “immunosuppressive” doses of glucocorticoids initially (i.e., 2 – 4 mg/kg prednisolone equivalent per day). Glucocorticoid doses can usually be tapered over weeks to months, and some animals may be completely weaned from steroids over time. The difficulty with these diseases is that most of them have (more common) infectious differentials that must be considered likely until appropriate diagnostic sampling and analysis is performed (i.e., CSF tap, fine needle aspirates, bronchoalveolar lavage). Glucocorticoids should be used with caution if infectious etiologies have not been ruled out.

**Hematopoietic neoplasia – lymphoma, leukemia, multiple myeloma, mast cell tumor:** Glucocorticoids are commonly used in conjunction with chemotherapy to treat hematopoietic neoplasia. At induction, canine and feline patients are commonly treated with dexamethasone or dexamethasone sodium phosphate 0.2 – 0.25 mg/kg by injection. If the patient is to receive L-asparaginase concurrently, the dose can be given before the L-asparaginase to decrease the likelihood of an anaphylactoid response. Patients with these round cell tumors often continue to receive prednisone or prednisolone oral therapy (2 mg/kg PO daily) as part of the chemotherapeutic regime. A definitive
diagnosis should be made prior to institution of glucocorticoid therapy. Once the steroids have been started, inability to “find the cancer” doesn’t mean it wasn’t there prior to therapy.

*Hypercalcemia*: Glucocorticoids decrease calcium absorption from the GI tract and aid in renal calcium excretion. When possible, serum ionized (rather than total) calcium concentrations should be used to make the diagnosis. Patients with clinical signs (including azotemia, weakness, GI disturbance, tremors, facial pruritus) referable to a demonstrated hypercalcemia can be treated with steroids as follows: dexamethasone 0.1 – 0.22 mg/kg or prednisolone 1 – 2.2 mg/kg every twelve hours. Other appropriate emergency therapy for hypercalcemia should also be instituted (treatment of the underlying disorder, fluid therapy, furosemide).

*Insulinoma*: Glucocorticoids induce glycogenolysis and peripheral insulin resistance. Therefore, they are often used to support blood glucose concentrations in patients with hypoglycemia due to insulinoma. The most common method is with oral or injectable prednisolone 0.25 mg/kg twice daily, titrated to effect, with a treatment goal to control of clinical signs rather than euglycemia.

*As an adjunct in severely inflammatory, infectious disease*: Sometimes “anti-inflammatory” doses of glucocorticoids may be beneficial in severe inflammation associated with certain infectious diseases. In general, glucocorticoids should be withheld from animals with infections, except in salvage situations in which the secondary inflammation is suspected to be the major cause of clinical signs. For instance, glucocorticoids are the recommended treatment for airway hypersensitivity in dogs with heartworm, and are the mainstay of therapy for cats with the disease. Steroids have also been used (in conjunction with appropriate antimicrobial therapy) to manage signs associated with cerebral edema due to fungal infections of the central nervous system; to decrease tracheal inflammation in dogs with infectious tracheobronchitis; and to treat the immune-mediated attack of red blood cells or platelets in dogs with tick-borne infections.

*Other possible indications*: Single, “anti-inflammatory” doses of dexamethasone (0.1 – 0.2 mg/kg) or prednisolone (0.5 – 2 mg/kg) are often used in patients with acute inflammatory conditions such as arytenoid edema and inflammation secondary to upper airway obstruction, or urethral inflammation and edema secondary to feline urethral obstruction. No specific evidence is available to prove benefit, but a single low dose in a patient with no contraindication (see below) may be helpful and potentially life saving in these situations.

Low doses of prednisolone (i.e., 0.2 – 0.5 mg/kg twice daily) may also be used to stimulate appetite in hospice-care situations. Steroids should not be used to stimulate appetite in lieu of an appropriate diagnostic work-up and directed treatment plan.

Dogs and cats with intracranial lesions that have significant associated cerebral edema may benefit from “anti-inflammatory” doses of steroids. This approach is particularly useful if the owner declines definitive diagnostics or treatment. Similarly, dogs with spinal pain that are known or suspected to have intervertebral disc disease but show no significant neurologic deficits may be treated with a short course (i.e., 1 – 2 weeks) of “anti-inflammatory” prednisone at 0.5 – 1 mg/kg twice daily on a tapering schedule along with 4-8 weeks of cage rest. Nonsteroidal anti-inflammatory drugs may be as effective in this population with fewer adverse effects.

A syndrome of critical illness-related corticosteroid insufficiency (CIRCI) has been described in humans with septic shock and other critical illnesses. People with CIRCI have improved shock reversal (improved blood pressure) when treated with low doses of hydrocortisone (approximately 1 mg/kg hydrocortisone every 6 hours) for 5 – 7 days; mortality benefit is still debated. Veterinary studies have identified CIRCI in septic dogs, and preliminary data suggest the syndrome also occurs in cats. It is unknown whether dogs and cats with CIRCI would benefit from low-dose hydrocortisone therapy.
There are numerous other conditions for which glucocorticoids were historically used to treat veterinary patients, such as general trauma, head trauma, and hypovolemic and hemorrhagic shock. A large, multicenter, double-blinded, placebo-controlled trial of steroids in humans with traumatic brain injury showed increased mortality in patients treated with steroids. Clinical trials in humans have failed to show survival benefit when steroids are used to treat hypovolemic or hemorrhagic shock. Steroids are not recommended for the treatment of shock or sepsis, except in the specific circumstance of volume-loaded, pressor-resistant hypotension in septic shock (CIRCI), as mentioned above. Thus, steroids are no longer recommended for the treatment of general trauma, head trauma, hypovolemic or hemorrhagic shock, or simple sepsis, and are only occasionally indicated in patients with septic shock. Though there is evidence for use of steroids in humans with acute spinal cord injury, the veterinary community debates the applicability of these findings to dogs and cats.

ADVERSE EFFECTS

Adverse effects of glucocorticoids are numerous, and their full discussion is outside the scope of these proceedings. Potentially life-threatening effects include immunosuppression and increased incidence of infection; poor wound healing; possibly gastrointestinal ulceration and perforation (definitely and particularly when combined with NSAIDs); thrombosis; pancreatitis; and iatrogenic hyperglycemia with a possible diabetes mellitus-like state.

CONTRAINDICATIONS TO GLUCOCORTICOID USE

Glucocorticoids are commonly considered contraindicated in animals with diabetes mellitus, pancreatitis, most infections, gastrointestinal ulceration (except when the ulceration is secondary to disease that is steroid-responsive), or in those receiving an NSAID. Ophthalmic steroids are contraindicated in animals with corneal laceration or ulceration.

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REFERENCES


