SA242
GLUCOCORTICOIDS: WHAT, WHERE, WHEN, WHY AND HOW?
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Glucocorticoids, mechanisms of action
Glucocorticoids (GCs) increase the circulating pool of mature neutrophils (PMNs) due to release of PMNs from the marginal pool which decreases migration into inflamed tissues. The effect is due to decreased expression of adhesion molecules, reduced adhesion to the vascular epithelium, and reduced movement through the vasculature into the tissues. Anti-inflammatory doses of GCs affect PMN trafficking more than function as minimal effects on phagocytosis and lysosomal stability occur. GCs decrease the circulating pool of lymphocytes, monocytes, eosinophils, and basophils primarily due to their movement from the vasculature to the lymphoid tissues. GCs alter the function of macrophages and other antigen presenting cells by reducing the cells ability to respond to antigens. The ability of macrophages to engulf and kill microorganisms is markedly inhibited. The production of cytokines such as TNF-α, interleukin-1 (IL-1), metalloproteinases, and plasminogen activator by macrophages are also markedly inhibited. GCs also decrease the production of IL-12 and interferon-γ by lymphocytes and macrophages which are important inducers of T-helper cell activity and cellular immunity. T-cells are more affected by GCs then B-cells with minimal effects on B-cell production of immunoglobulins at anti-inflammatory doses. However, high doses of GCs can decrease immunoglobulin production.

GCs also reduce the production of prostaglandins and leukotrienes by the arachidonic acid pathway. The primary effect on the arachidonic acid pathway is thought to be through inhibition of phospholipase A2, but some effects on cyclooxygenase-2 (COX-2) may also occur. GCs also have a variety of effects on blood vessels. GCs improve the microvascular integrity and circulation, and decrease vessel permeability. It is unclear as to the precise mechanisms by which these effects occur, but may be due to inhibition of vasoactive substances such as histamine, serotonin, and prostaglandins among others. The vascular effects have not been identified as a clinical benefit.

Glucocorticoids, adverse effects
Adverse effects are expected with both short-term and long-term administration of GCs. The most common adverse effects with administration include the polyuria, polydipsia, and polyphagia. Other effects with GC administration include osteoporosis, myopathy, inhibition of fibroblast activity, decreased intestinal calcium absorption, pancreatitis, gastric ulceration / perforation, colonic ulceration / perforation, sodium retention, fluid retention, hyperlipidemia, lipolysis, protein catabolism, fatty infiltration of the liver, steroid hepatopathy, anti-insulin effects, decreased thyroid hormone production, increased parathyroid production, decreased host response to bacterial infections, and increased rates of cystitis. Case reports have been published detailing acute episodes of congestive heart failure after GC administration to animals with subclinical and undiagnosed cardiac disease which is probably due to fluid and sodium retention and hypertension. A study examining the effects of shock doses of methylprednisolone sodium succinate on animals presenting for spinal surgery resulted in

36/40 animals being identified as having GIT bleeding despite administration of cimetidine, sucralfate, or misoprostol. Therefore it is not unreasonable to expect GIT injury with administration of shock doses of GC for spinal injury. Shock doses of corticosteroids produce euphoria in human patients. The euphoric effect is probably the reason most animals “look better” after administration of shock doses of corticosteroids and typically is not an indication that the shock doses are beneficial. Opioid administration can also produce euphoric effects and make animals “look better” with less adverse effects than shock doses of GCs.

Specific glucocorticoids

Prednisolone is the active form of the glucocorticoid whereas prednisone is inactive and must be metabolized to prednisolone to elicit an effect. In dogs, prednisone is well metabolized to prednisolone after administration and as such prednisone is a very good choice for oral glucocorticoid therapy. In contrast, cats do not appear to metabolize prednisone to prednisolone well and as such have variable and inconsistent effects from oral prednisone. Prednisolone is a better choice than prednisone for oral administration to cats. In comparing prednisone / prednisolone to dexamethasone, dexamethasone is approximately 7-10 times more potent meaning an equivalent dose of dexamethasone should be $1/7^{th}$ to $1/10^{th}$ the dose of prednisone. Prednisolone and prednisone produce some mineralocorticoid effects (sodium and water retention) and therefore can exacerbate conditions of fluid retention like congestive heart failure with pulmonary edema. In contrast, dexamethasone has minimal effects of sodium and fluid retention and may be a better choice if fluid retention is contraindicated. Dexamethasone produces a longer duration of effect, at least 32 hours of adrenal suppression, after a single dose in dogs compared to <24 hours for prednisone/prednisolone. Dexamethasone also appears to be more likely to cause GI adverse effects than prednisone / prednisolone.

Glucocorticoids, dose-dependent effects

Glucocorticoid dosages depend on the condition that is being treated. Glucocorticoid dosages can be classified as physiologic replacement, anti-inflammatory, immunosuppressive, and shock doses.

Physiologic dosages are designed to supplement or replace the amount of endogenous cortisol produced in a 24-hour period. Prednisone or prednisolone is administered at 0.2 mg/kg/d for replacement therapy. Anti-inflammatory dosages of glucocorticoids are commonly administered for conditions such as atopy, angioedema, and urticaria. The anti-inflammatory dosages of prednisone / prednisolone in dogs is 1-2 mg/kg/d and for dexamethasone 0.1-0.2 mg/kg/d. The anti-inflammatory dose in cats is approximately twice that of dogs. Immunosuppressive dosages are administered for conditions such as autoimmune hemolytic anemia and immune mediated thrombocytopenia. Prednisone administered at 2-6 mg/kg/d and dexamethasone 0.3-1 mg/kg/d are immunosuppressive dosages. Most animals respond to the lower end of the dosages for immunosuppression therapy. The shock dosage of methylprednisolone sodium succinate is 30 mg/kg IV. There currently no indications (no clinical benefits demonstrated) for shock doses of dexamethasone in dogs or cats (see below).

Efficacy of shock doses of glucocorticoids

Head trauma. A recent study in humans demonstrated an increased mortality rate in patients receiving shock doses of methylprednisolone sodium succinate as compared to groups that did not receive GCs. There are no large studies in animals assessing the effects of GCs on head trauma, but extrapolation from human data indicate GCs are NOT indicated in the acute management of head trauma in animals.

Spinal trauma. There are conflicting opinions on the benefit of shock doses and GC use in spinal trauma. A study in 1990 indicated a benefit to shock dose methylprednisolone sodium succinate (MPSS) in spinal trauma, but criticisms of the study soon followed as to its applicability and limitations. Experimental models have produced positive results for GC use in spinal trauma, but doses were administered prior to experimental injury or within a short period of time following injury. ***Clinical cases of IVDD in dogs, pre or postoperative administration of glucocorticoids provided no benefit compared to animals not treated with GC's***, but increased adverse effects were seen in GC treated dogs. There is conflicting data supporting the use of GC in spinal trauma, although they are widely used. Currently, most people recommend shock doses of Solu Medrol only within 8 hours of spinal trauma.

Generalized trauma / Heat Stroke. There is no data supporting the use of GC in generalized trauma (i.e. hit by car, dog fights, etc.) or heat stroke. In fact GC may increase morbidity and mortality due to the numerous adverse effects. Supportive care such as crystalloids and colloids, pain management with opioids, and body temperature are the primary recommendations along with stabilization of blood loss and fractures. Antimicrobials may also be indicated.

Sepsis / endotoxemia. Most studies investigating the use of GC in sepsis and endotoxin models are poorly translated into clinical practice. Most of the models have administered GCs prior to exposure or immediately following exposure. Shock doses GCs may increase the morbidity and mortality in sepsis due to the immunosuppressive effects and beneficial effects have not been demonstrated clinically. Shock doses in endotoxemia also do not result in decreased mortality or morbidity, however physiologic doses may be beneficial (i.e. 0.2 mg/kg methylprednisolone), but there is not a consensus on their use.

Anaphylaxis. GCs are indicated for the treatment of anaphylactic reactions. However ***immunosuppressive*** doses are recommended (i.e. 2-6 mg/kg IV MPSS OR 0.3-1 mg/kg dexamethasone), not shock doses. If cardiovascular collapse is present administration of epinephrine (2.5-5 mcg/kg {0.0025-0.005 mg/kg} IV) will provide immediate cardiac stimulant and vasopressor effects.

Addison's Crisis. GCs are recommended for the treatment of animals in an Addison's (hypoadrenocorticism) crisis, although ***immunosuppressive*** dosages are recommended initially (2-6 mg/kg MPSS). The primary focus in stabilizing animals is to correct the hyperkalemia and hyponatremia. Normal saline is the fluid of choice for dehydrated animals with hyperkalemia and hyponatremia.

Disclaimer: References available on request. The information is accurate to the best of the author's knowledge. However recommendations change as new data become available and errors are possible. The author recommends double checking the accuracy of all information including dosages.