Use of Corticosteroids in Equine Practice

Thomas J. Divers, DVM, DACVIM, DACVECC

Corticosteroids, more specifically glucocorticoids, are a group of potent anti-inflammatory and immunosuppressive drugs that are frequently used in horses; often resulting in beneficial but sometimes adverse effects. Glucocorticoids bind to glucocorticoid receptors and exert their clinical effect at the cellular level by interfering with or decreasing the expression of pro-inflammatory proteins/genes (NF-$_K$B, MAPK P38, phospholipase A_2,) inflammatory cytokines etc.) without decreasing selected anti-inflammatory proteins (e.g., IL-10).[1,2,3] Anti-inflammatory proteins may even be increased with glucocorticoid treatment. Glucocorticoids also interfere with leukocyte adhesion, phagocytosis, and cellular respiratory burst along with decreasing both humoral and cell-mediated immunity.[1,3] Anti-inflammatory actions of glucocorticoids via upregulation and downregulation of genes may require hours while other non-genetics action of glucocorticoids can occur in minutes, eg. modulation of reactive oxygen species and stabilization of membranes and smooth muscle activity. Anti-inflammatory or immunosuppressive potency of glucocorticoids in relative potency are hydrocortisone 1 (natural cortisol 0.8), prednisolone 4 (methylprednisolone 6), dexamethasone 25 or greater, and triamcinolone 5 (although some preparations are much higher).[4] These numbers do not always relate to the *in vivo* effects in horses as, for example, prednisolone at 20-40X the dexamethasone dose was inferior to dexamethasone for treating equine asthma.[5] The T½ of glucocorticoids is short for hydrocortisone (8 hours), moderate for prednisolone (q 24 hours) and greater for dexamethasone (36+ hours). Glucocorticoids can be administered by the intravenous (IV), intramuscular (IM), oral (PO) route, or by rapid inhalation, nebulization, local injection (intra-articular, cervical facet), or by topical application (ophthalmic, skin). The most commonly used parenterally-administered glucocorticoids in equine practice are prednisolone, dexamethasone, and triamcinolone acetonide. Prednisone is not recommended for oral use in the horse because of extremely low bioavailability. The bioavailability of dexamethasone and prednisolone are approximately 50% depending upon individual products.[3] Injectable dexamethasone can be given PO although the bioavailability was quite variable between horses and highest when administered to fasted horses.[6] The FEI detection time of Dexamethazone after IV administration is approximately 48 hrs. Methylprednisolone acetate and triamcinolone acetonide can be used IM or IA when prolonged duration of effect is desirable. Their FEI detection times following joint injection are approximately 28 and 7 days respectively. Fluticasone propionate and beclomethasone are the most commonly used glucocorticoids for rapid inhalation in horses.[7] Injectable dexamethasone (5 mg) can be used for nebulization.[8] although recent data from the laboratory of Dr. Jean-Pierre Lavoie in Montreal did not find any efficacy with this treatment in asthmatic horses (Equine Vet J. 2019). Administration of glucocorticoids by inhalation or nebulization results in low systemic absorption but should be expected to suppress serum cortisol and FEI detection is approximately 7 days or less. Budesonide is a potent corticosteroid used for human asthma. The nebulized dose in the horse is approximately 1-3 ug/kg q 12 hr but I believe this is an FEI banned substance.

The systemic administration of glucocorticoids in horses is considered standard of care for a variety of immune-mediated diseases such as; asthma, vasculitis, immune-mediated anemia or thrombocytopenia, a variety of skin disorders including pemphigus, hypersensitivity reactions and immune mediated myositis and uveitis. Horses with suspected immune mediated inflammatory bowel disease should be treat with parenterally administered glucocorticoids until there is clinical and laboratory improvement before switching to oral administration.[3] Glucocorticoids are also used as short-term anti-inflammatory treatment and to decrease tissue

swelling for selected surgical procedures such as throat surgery, following myelograms to decrease inflammation and fever, and in life-threatening localized inflammatory diseases such as meningitis, severe chemical induced aspiration pneumonia, herpes myelitis and acute lymphangitis. High dose glucocorticoids (dexamethasone) can be used in late term pregnant mares suffering from a life threatening disorder to enhance maturation of the fetus.[9] The beneficial use of glucocorticoids in shock and acute central nervous system injuries has not been accepted in human medicine, but corticosteroids are commonly used in horses with these disorders and due to individual case responses, their continued use by equine practitioners is likely.[10] Cortisol (hydrocortisone, 0.2 mg/kg/every 4 hrs. Hart. K. Pediatr Res. 2011) treatment is used for treating relative adrenal suppression mostly as a result of refractory septic shock in foals. Glucocorticoids are also used as singular or multidrug treatment for lymphoma in horses.

Local injections of glucocorticoids are mostly intra-articular treatment for osteoarthritis, while topical administration is most commonly used for conjunctivitis, uveitis, and non-ulcerative keratitis although they are recommended for eosinophil ulcerative keratitis. Glucocorticoids are also sometimes mixed with antibiotics for “throat sprays” or for distal limb “scratches”. Triamcinolone acetonide, betamethasone acetate and methyl- prednisolone acetate are depot formulations and are most commonly used for intra-articular (IA) and cervical facet injections. Triamcinolone acetonide has been shown to be chondroprotective while methy-prednisolone acetate can cause cartilage degradation. Triamcinolone is more rapidly absorbed into systemic circulation by IA injection than by I.M injection and reaches a higher peak serum level by the I.A. route. Serum levels are below level of detection much quicker with IA injections in comparison to IM injections. Synovial fluid triamcinolone levels are usually undetectable following I.M administration.

The best researched use of glucocorticoids in equine practice is for asthma.[11] Glucocorticoids are the drug of choice for treating equine asthma and dexamethasone has been documented to be the preferred corticosteroid for severe asthma. Parenterally administered glucocorticoids are recommended for severe asthmatic episodes, while inhalation therapy can be used for maintenance therapy or treatment of mild asthma. Beclomethasone and Ciclesonide are both prodrugs that have to be activated by esterase enzymes within the lung to have glucocorticoid effects. These drugs have minimal systemic absorption. Ciclesonide is approved for use in horses given via a mist inhaler and does not suppress serum cortisol.[14]

Intra-articular injections of triamcinolone acetonide improves lung function in horses with severe asthma and has an effect that persists even after TA serum concentration is below the quantification level that is employed as a threshold by the International Association of Racing Commissioners.[12]

Extended corticosteroid treatments are often required in horse with conditions such as inflammatory bowel disease (IBD), allergic dermatitis and asthma. For long-term oral corticosteroid treatment it is preferred that treatments be administered in the morning to “lessen” the effect on serum cortisol.

Adverse effects of glucocorticoids are well known.[1,3] Immunosuppression predisposing to bacterial or fungal (pulmonary, intestinal and ocular) infections, decreased wound healing and insulin-resistant laminitis are the most serious adverse events. Other less severe but notable adverse effects include muscle wasting, hyperglycemia and polyuria/polydipsia and rarely gastric ulcers or hepatic lipidosis.[3,4] Within 12 hours of glucocorticoid administration, blood neutrophil counts may increase and lymphocytes decrease. Although neutrophil numbers are increased, glucocorticoids cause a decrease in neutrophil function (phagocytosis and adhesion). Horses receiving glucocorticoids are known to have decreased immune response to infection and vaccines. Numerous studies have evaluated the risk of laminitis in horses receiving corticosteroids and most have been unable to prove an association.[13] Regardless, practitioners know that it can happen! Horses that have insulin dysregulation (equine metabolic syndrome [EMS]) are likely predisposed to laminitis as an adverse event following glucocorticoid

administration. Duration of insulin resistance following “commonly used doses of individual corticosteroids are longest following triamcinolone administration (c7 days), shortest following prednisolone (c1 day) and intermediate (c3 days) following dexamethasone administration; hydrocortisone may have no effect. Single doses of dexamethasone appear to be unlikely to cause laminitis when used in equines with EMS. Horses with EMS or Cushing’s disease requiring glucocorticoid treatment are best treated with prednisolone unless the condition is life-threatening in which case dexamethasone should be used. When horses are treated with glucocorticoids for an extended time, tapering of the dose over time should be performed to prevent adrenal insufficiency syndrome. Single doses (0.044mg/kg) of dexamethasone and triamcinolone will immediately suppress cortisol production and some suppression is noted for approximately 5 and 10 days respectively. Electrolyte imbalances, especially hypokalemia, may occur following glucocorticoid treatments.

An alternative immunosuppression treatment for horses at risk of laminitis would be azathioprine.[3] Azathioprine interferes with DNA and RNA formulation by inhibiting purine synthesis and has been successfully used in several immune-mediated disorders and with rare adverse events. I have most frequently used this drug in life-threatening cases of immune-mediated hemolytic anemia or thrombocytopenia; I often use both dexamethasone and azathioprine until there is sufficient improvement in the laboratory values.

References

1. Felippe M. Julia B. Immunosuppressive therapy in Equine Clinical Immunology; Felippe M. Julia B., Wiley-Blackwell Ames Iowa 2016; 237-238.
2. Goppelt-Struebe M, Woltler D, Resch K. Glucocorticoids inhibit prostaglandin synthesis not only at the level of phospholipase A2 but also at the level of cyclo-oxygenase/PGE isomerase. Br J Pharmacol 1989; 98:1287-1295.
3. Leclere M. Corticosteroids and immune suppressive therapies in horses. Vet Clin North Am Equine Pract 2017; 33:17-27.
4. Pereira MM, Groover E, Wooldridge A, et al. Review of glucocorticoid therapy in horses. Part 2: Clinical use of systemic glucocorticoids in horses. Equine Vet Educ 2018; 30:213-224.
5. Leclere M, Lefebvre-Lavoie J, Beauchamp G, Lavoie JP. Efficacy of oral prednisolone and dexamethasone in horses with recurrent airway obstruction in the presence of continuous antigen exposure. Equine Vet J. 2010; 42(4):316-21.
6. Grady JA, Davis EG, Kukanich B, Sherck AB.Pharmacokinetics and pharmacodynamics of dexamethasone after oral administration in apparently healthy horses. Am J Vet Res. 2010;71(7):831-9.
7. Bullone M, Vargas A, Elce Y, et al. Fluticasone/salmeterol reduces remodeling and neutrophilic inflammation in severe equine asthma. Sci Rep 2017; 7:8843.
8. Haspel AD, Giguère S, Hart KA, et al. Bioavailability and tolerability of nebulised dexamethasone sodium phosphate in adult horses. Equine Vet J 2018; 50:85-90.
9. Ousey JC, Kolling M, Kindahl H, et al. Maternal dexamethasone treatment in late gestation induces precocious fetal maturation and delivery in healthy Thoroughbred mares. Equine Vet J 2011; 43:424-429.
10. Werners AH. Treatment of endotoxaemia and septicaemia in the equine patient. J Vet Pharmacol Ther 2017; 40:1-15.
11. Calzetta L, Rogliani P, Page C, et al. Clinical effect of corticosteroids in asthma-affected horses: a quantitative synthesis. Equine Vet J 2018; Feb 2. Epub ahead of print
12. Bessonnat A, Picotte K, Lavoie JP. Intra-articular triamcinolone acetonide improves lung function in horses with severe asthma. Equine Vet J. 2020 Jan;52(1):131-135.
13. Bailey SR. Corticosteroid-associated laminitis. Vet Clin North Am Equine Pract 2010; 26:277-285.

14. Lavoie JP, Bullone M, Rodrigues N, Germim P, Albrecht B, von Salis-Soglio M
Effect of different doses of inhaled ciclesonide on lung function, clinical signs related to airflow limitation and serum cortisol levels in horses with experimentally induced mild to severe airway obstruction. Equine Vet J. 2019 ;51(6):779-786.

A recently published recommended review: Mainguy-Seers S, Lavoie JP. Glucocorticoid treatment in horses with asthma: A narrative review. *J Vet Intern Med*. 2021;35(4):2045-2057. doi:10.1111/jvim.16189