Pharmacology Review: The Corticosteroids

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The physiological importance of the adrenal cortex was recognized over 100 years ago, and by the 1930s crude adrenal extracts were being used in human medicine. Over the next 20 years, the synthesis and chemical structures of the major natural and synthetic steroids were elucidated and the principles of their pharmacology and therapeutics worked out. Today, the natural and synthetic corticosteroids can be divided into three main groups based on their pharmacological characteristics. The first and most important group for the equine practitioner is the glucocorticoids, which predominantly affect protein and carbohydrate metabolism and produce the potent anti-inflammatory effects of these drugs. The second group is the mineralocorticoids, represented in nature by aldosterone, which gives rise to sodium and water retention. The third group consists of the adrenal sex hormones.[4] Because the glucocorticoid actions of the corticosteroids are those with which the equine practitioner is primarily involved, this review will be devoted to those actions of the corticosteroids. Table 1 shows the relative anti-inflammatory effectiveness of some natural and synthetic corticosteroids and how effective the selection, for anti-inflammatory action among the synthetic glucocorticoids, has been.

TABLE 1

Relative potency of corticosteroids.

	Sodium retention	Anti-inflammatory effect
Natural Steroids:		
Cortisol	1	1
Corticosterone	15	0.3
Synthetic Steroids:		
Prednisolone	0.8	4
Dexamethasone	0	25
Flumethasone	0	700

Plasma Level and Control

Cortisol and corticosterone are the principal glucocorticoids found in equine plasma, at levels of about 70 ng/ml, and 5 ng/ml, respectively.[5] Their rate of secretion in the horse is not known, but is probably comparable with the 0.5 to 1 mg/kg/day secreted by the dog and human. Secretion of cortisol by the adrenal cortex is under direct control of the adrenocorticotropic hormone (ACTH) of the anterior pituitary, and administration of ACTH brings about a prompt increase in plasma cortisol concentration. After administration of 200 units of ACTH, equine plasma cortisol levels peak at about 150 ng/ml five hours after dosing, and then decline toward control over the next 30 hours (Figure 1). Since cortisol is not stored in the adrenal cortex, the rate of secretion is also the rate of formation of this hormone, and both are directly controlled by ACTH.[4]

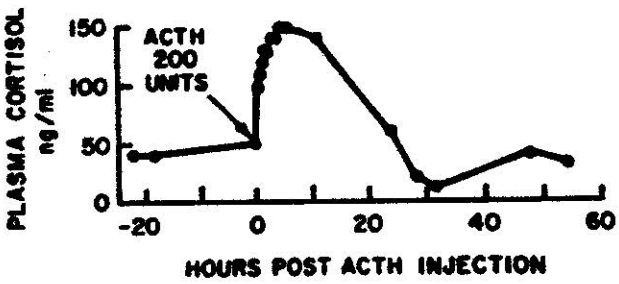

Figure 1. Effect of ACTH on plasma cortisol in the horse. The solid circles (•-•) show plasma levels of cortisol before and after intramuscular injection of 200 units of ACTH gel in a pony (adapted from Jones[5]).

The rate of release of ACTH from the pituitary is influenced by a number of factors: exercise, stress, surgery, cold exposure, hypoglycemia, etc. The most important control on natural ACTH release, however, is feedback inhibition by high plasma levels of cortisol or its synthetic analogues. This gives rise to the major problem with prolonged corticosteroid therapy, which is "feedback inhibition" of ACTH release, resulting in reduced adrenal cortex function and finally in atrophy of the adrenal cortex. If corticosteroid therapy is abruptly terminated, the animal is left with reduced or no natural corticosteroids which can be fatal.[4] In a milder form this may cause the "turning out" syndrome, which is seen when horses are "turned out" after a racing season during which they received large doses of corticosteroids. These horses tend to be un-

thrifty, dull, depressed, and to show mild anemia despite good care.* It may take several months, after prolonged treatment with corticosteroids, to recover full adrenal function.

Once released from the adrenal, the corticosteroids travel in the bloodstream to their cellular sites of action. The corticosteroids are bound in the cytoplasm of their "target" cells to specific protein receptor molecules, which bind corticosteroids very tightly.[12] When they bind steroids, the configuration of these receptor molecules changes, and the altered complex migrates into the cell nucleus (Figure 2). These receptor complexes then bind to the nucleus and initiate transcription and the formation of new messenger RNA (mRNA).[11] This mRNA migrates out of the nucleus, binds to the ribosomes, and gives rise to new protein synthesis, which redirects the function of the cells involved. Thus, the initial action of all steroid hormones is new protein synthesis, even though the subsequent actions of these proteins may lead to cellular breakdown or death.[4]

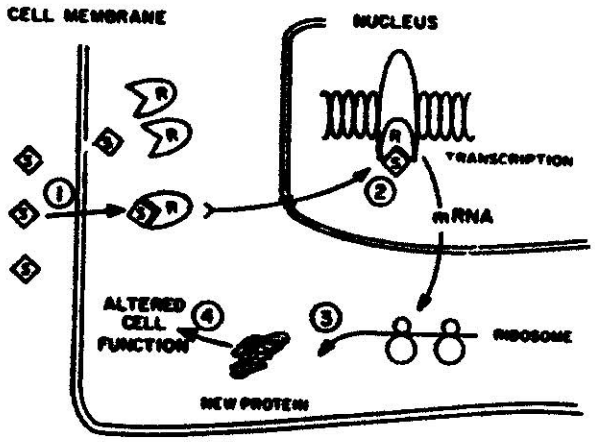

Figure 2. Action of steroids at the cellular level. Steroid drug molecules (s) enter the "target" cells, bind to specific receptors, and change the shape of these receptors (1). This drug-receptor complex then diffuses into the nucleus, binds to receptor sites on the genes, and initiates transcription (2). The newly formed mRNA diffuses out of the cell, binds to the ribosomes, and gives rise to new proteins (3) which redirects the function of the cell (4) (modified from O'Malley[11]).

Action on Intermediary Metabolism

The action of the glucocorticoids on protein, carbohydrate, and fat metabolism illustrates the complex actions of this group of drugs. The glucocorticoids cause a breakdown (catabolism) of muscle protein and thus an increase in blood levels of amino acids and increased utilization of these amino acids by the liver. In turn, in the liver, more glycogen is laid down and glucose synthesized and released into the bloodstream.[4] Because the peripheral utilization of glucose is also reduced, blood glucose levels rise rapidly, peaking at about 24 hours after a dose of fluprednisolone acetate in cattle.

For all corticosteroids and their derivatives studied to date, it has proved impossible to separate the effects on protein and carbohydrate metabolism from the anti-inflammatory effects of these drugs. It therefore appears likely that the effects on intermediary metabolism and inflammatory reactions are different facets of the same fundamental processes.[4]

While low levels of the corticosteroids are required to allow adrenergic lipolysis, high levels of corticosteroids produce a very specific redistribution of fat in the human. Humans maintained on high doses of steroids accumulate fat around the face ("moon-face") and on the back of the neck ("buffalo hump").[4] Whether or not a special pattern of fat redistribution in response to the corticosteroids occurs in the horse has not been reported.

The Blood Picture

The glucocorticoids have very specific effects on the blood picture, producing what is called the glucocorticoid hemogram. The number of circulating eosinophils (Figure 3), lymphocytes, and basophils declines abruptly. On the other hand, the number of polymorphonuclear leukocytes in the blood is increased, apparently due to increased release combined with decreased removal from blood. The glucocorticoids tend to increase the hematocrit somewhat, but prolonged therapy with them is markedly lympholytic. In the rat, dissolution of lymphocytes in lymphoid tissue rapidly becomes apparent, with nuclei becoming pyknotic and disintegrating, and cells shedding their cytoplasm. If therapy is maintained, the lymph nodes, thymus, and spleen involute, and it is

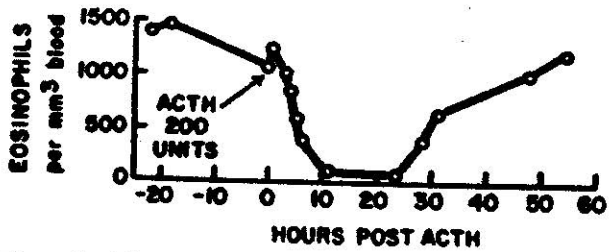

Figure 3. Effect of ACTH on eosinophil count in the horse. The open circles show the blood eosinophil count before and after intramuscular injection of 200 units ACTH gel in a pony (adapted from James[5]).

* Gabel, A. A., personal communication, The Ohio State University.

this effect which leads to the use of glucocorticoids in certain types of lymphoma.

Despite the fact that glucocorticoids do not affect the titer of circulating antibodies, they have marked effects on the immune response. The symptoms of certain allergic states are often dramatically reduced by the corticosteroids. The corticosteroids are particularly useful in preventing the consequences of cell-mediated (delayed hypersensitivity) immune reactions such as graft rejection.[4]

Effects on Growth and the Central Nervous System (CNS)

The glucocorticoids have marked effects on both growth and the central nervous system. Their antianabolic effect appears as a suppression of growth, which is a widespread effect of the glucocorticoids. In the fully grown animal this same effect is seen as a delay in wound healing. The glucocorticoids also increase the rate of demineralization of bone, and prolonged administration can lead to osteoporosis and compression fractures. In the CNS, the glucocorticoids produce an antipyretic effect similar to that of the nonsteroidal anti-inflammatory drugs. Unlike the nonsteroidal group, however, large doses of the glucocorticoids can cause an elevation of mood and euphoria, and this effect has led to abuse of corticosteroids by humans.[4]

Effects on Water and Electrolyte Metabolism

In general, the potent glucocorticoids have minimal effects on water and electrolyte metabolism, and even large doses do not affect these parameters. However, excessive administration of glucocorticoids with significant mineralocorticoid activity leads to sodium and water retention. Continued administration can result in edema, hypokalemia and metabolic alkalosis. Excessive administration of corticosteroids will thus result in muscle weakness from both protein catabolism and hypokalemia.

Anti-Inflammatory Effect

The glucocorticoids, and particularly the potent synthetic members of this group, have the capacity to prevent or suppress the local heat, redness, swelling, and pain by which inflammation is grossly recognizable. At the microscopic level, they inhibit both the early and late phases of the inflammatory process. In the early phases they inhibit edema formation, fibrin deposition, capillary dilation, and the migration of leukocytes and phagocytic activity. They also inhibit the later stages, such as capillary and fibroblast proliferation and cicatrization. The precise mechanisms of these effects are not well understood, but the corticosteroids produce these effects quite independent of the type of agent which elicits the response.[4] The effect is therefore a suppression of the tissue response to trauma rather than any direct antagonism of the causative agent.

Because the anti-inflammatory effect simply suppresses tissue response, treatment with corticosteroids in no way neutralizes or removes a primary cause, but merely suppresses clinical signs of the disease. This suppression of clinical signs is the most dangerous aspect of corticosteroid therapy. A patient with severe bacterial pneumonia treated with corticosteroids may appear to improve, and an inflamed joint injected with corticosteroids will appear normal, and the horse will be improved or go sound. In truth, however, both conditions progress at at least the same rate as they would have in the absence of corticosteroids, and collapse, when it does occur, is sudden and without warning. This aspect of the action of the corticosteroids has given rise to the grim comment that "a patient on corticosteroids can walk all the way to the autopsy room." Similarly, a horse can wear a joint surface right down to the bone by running on a glucocorticoid-injected joint.

Therapeutic Uses of Corticosteroids

Two main guidelines have been developed covering use of the corticosteroids which should be kept in mind when these drugs are used: (1) a single large dose of a corticosteroid, or even therapy for a few days, is unlikely to produce harmful effects; (2) prolonged corticosteroid therapy, to the extent that the dose exceeds substitution therapy, can produce potentially lethal effects, especially if therapy is abruptly withdrawn.[4]

These rules lead to the principle that long-term maintenance on corticosteroid therapy is reserved for serious or life-threatening diseases, while short-term therapy is more easily justified.[4]

Systemic Corticosteroids

Because of the ability of glucocorticoids to suppress the immune response, they should be used with great care in the presence of bacterial or viral infections. Corticosteroids are commonly given in association with broad-spectrum antibiotic treatment of infections and, undoubtedly in this situation, will act to improve an animal's appetite and appearance, and reduce fever. Use of these drugs, however, carries the risks of blocking the animal's natural response and

giving rise to fulminating infection. It is difficult, therefore, to justify the indiscriminate use of glucocorticoids under these conditions.

Systemic corticosteroids were once widely used in the therapy of shock, but their efficacy in this situation is not clear. The evidence now suggests that their use should be limited to endotoxic shock, and there is good evidence to support their use in endotoxin shock in the horse. Another clear-cut use for systemic glucocorticoids is in treatment of cerebral edema where skillful use of these drugs can be lifesaving.

Local Corticosteroids

The corticosteroids are found in high concentrations in inflamed tissues, and their anti-inflammatory action depends directly on their concentration. When applied locally, therefore, they achieve high tissue concentrations and a very effective local anti-inflammatory effect. Local injection of corticosteroids into joints, tendons, or bursal spaces can give good relief of pain and return of function, in keeping with their actions on inflammatory changes of any origin. The ultimate outcome of such treatment, however, is determined largely by the amount of stress to which the injected area is subjected in the postinjection period. For best results, the corticosteroids should be used in conjunction with rest to allow complete healing with minimum scar tissue formation around the joint.[1,2] As a general rule, bursal injections of corticosteroids can be used with a minimum of postinjection rest. Thus, for example, injections into the cuneate tendon bursa, trochanteric bursa, and the bicipital bursa can be made and the horse may continue to race.

Injection of corticosteroids into inflamed joints needs considerably more care. In keeping with the rule that corticosteroids cannot affect the basic cause of the inflammation, the joint should first be examined radiographically and bacteriologically for primary causes such as bacterial infections, chip fractures, fractures involving the joint area, or villonodular synovitis.[4] Correction of such underlying causes greatly improves the prognosis in any joint problem, whether or not corticosteroids are administered. On the other hand, if chips or other inciting causes are not removed, the continued mechanical trauma will only cause further deterioration and necessitate reinjection of the joint. Continuation of this cycle results in eventual erosion of the joint surface, complete loss of joint function, and possible incapacitation of the animal for use even as breeding stock.

In a careful experimental study of the effects of intra-articular steroids on carpal chip fractures, Meagher[7] found much more rapid deterioration of joints injected with corticosteroids than noninjected joints. Although the injected joints initially showed less lameness and swelling than untreated joints, the healing process was delayed in the injected joints. In the uninjected joints, there was active bone production in the fracture area, and the healing process proceeded well. In the injected joints, however, considerable lysis of bone and cartilage was seen, and instead of production of new bone, there was demineralization at the fracture site combined with a periarticular fibrocartilage buildup around the injected joint. This type of response gives rise to the typical "productive-destructive" lesions characteristic of corticosteroid injected joints.[6]

In the second portion of this study the chip fractures were removed from both the injected and uninjected joints after the course of steroid therapy. Thirteen days after surgery, all of the corticosteroid-injected joints were hot, swollen, and painful, while no reaction was noted in the uninjected joints. Vigorous antibiotic therapy was commenced, and the infections were controlled. This sequel is consistent with the action of corticosteroids to suppress tissue response to injury and emphasizes the risks of performing surgery on tissues recently exposed to corticosteroids.

From this study Meagher concluded that joint deterioration after chip fracture was accelerated by corticosteroids, and that use of corticosteroids in the presence of chip fractures is contraindicated. Intra-articular steroids, however, were considered useful in soft tissue injury of a joint, but a period of at least 30 days rest should follow treatment. These authors also concluded that surgery on a corticosteroid-injected joint should not occur for at least eight weeks after the last treatment with corticosteroids.

In a somewhat less rigorous study on the intra-articular use of steroids in racing Thoroughbreds, McKay and Milne[6] reported on a series of 22 horses treated intra-articularly with corticosteroids. Unfortunately, these authors failed to detail the clinical conditions which prompted intra-articular injections of corticosteroids in these horses. Of the 22 horses treated, six showed radiographic evidence of deterioration in the joint subsequent to the initial radiographic examination, but in only one horse were signs of diminished joint-space and "productive-destructive" lesions on the lateral aspects of the joint seen. While these lesions were considered pathognomic for intra-articular corticosteroid injection, changes in the other six joints could not be distinguished from the normal progres-

sion of joint disease. The remaining 16 horses showed no radiographic evidence of deterioration. The authors interpreted these results to support a role for the careful and judicious use of intra-articular corticosteroids in racing horses.

In a detailed laboratory study of the effect of intra-articular glucocorticoids, Behrens *et al.*[2] observed gross and microscopic damage to articular cartilage after 12 weekly injections of hydrocortisone. In these animals the non-weight-bearing surfaces were not distinguishable from normal specimens, but the weight-bearing surfaces of the femur and tibial plateaus showed multiple yellowish lesions in 50% of the animals.

These observations led the authors to propose a sequence of changes in joint cartilage in response to intra-articular injection of steroids. The first step in this sequence was thought to be a massive decrease in the synthesis of all major cartilage matrix components. Among these components a loss of proteoglycan content in particular was thought to lead to a loss in cartilage stiffness. In non-weight-bearing areas the cartilage was able to maintain its structural integrity, while the mechanical stress in weight-bearing areas caused death of cells, cystic degeneration of matrix, and fissuring in the mid-zone areas of weight-bearing surfaces. Lysosomal enzymes released by dying cells were thought to potentiate this process. This suggested sequence of events for articular cartilage changes is summarized in Figure 4.

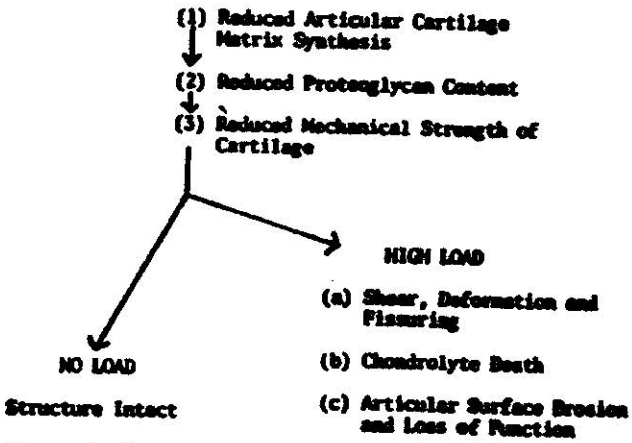

Figure 4. Proposed changes in joint cartilage after intra-articular glucocorticoids.

Local corticosteroid injections have also been used in the treatment of bowed tendon. Again, however, prolonged rest is required to insure as complete healing as possible. Despite the fact that the tendons may look very good within a few weeks, the temptation to race the horse should be avoided, and the horse should not be worked at race speed for about 12 months.

Adverse Responses to the Corticosteroids

The principal adverse response to glucocorticoids comes from their ability to suppress the inflammatory response. Thus, when applied locally, they leave the animal open to infection at the point of local application, usually an eye or a joint. In the eye, local corticosteroid treatment can mask the progression of bacterial, viral, or fungal diseases until sight is lost. Corticosteroids should not be used in the treatment of lacerations or abrasions of the eye as they delay healing and promote the spread of infection. Surgery in corticosteroid-treated joints is also dangerous, because healing is delayed, the would may open, and resistance of the joint to infection is markedly reduced. Most veterinarians will not operate on injected joints for at least six weeks after the last corticosteroid injection to avoid these complications.

When corticosteroids are systemically used in large doses, they leave the animal open to systemic infection. Injection of large doses of steroids are routinely used to render animals susceptible to specific experimental infections. If large doses of the corticosteroids are maintained for any sustained period of time (>2 weeks), suppression of ACTH release occurs and atrophy of the adrenal cortex occurs. One way of avoiding this problem is to administer short acting steroids intermittently on an every second or third day basis. This pattern of intermittent administration allows plasma levels of the steroid to drop, which stimulates the natural release of ACTH. An alternative maneuver is to administer exogenous ACTH with the steroid, to stimulate and maintain the function of the adrenal cortex.

The various corticosteroid preparations available to the veterinarian differ in regard to their potency, pharmacokinetics and therapeutic effects. Cortisol, cortisone, prednisolone and prednisone possess both mineralocorticoid and glucocorticoid activity. The newer synthetic drugs such as methylprednisolone, betamethasone, and triamcinolone are potent glucocorticoids, with few mineralocorticoid actions. The plasma half-lives of all the adrenal steroids are relatively short, with an apparent plasma half-life for cortisol of about 80 minutes. Long-acting steroid preparations are therefore slowly absorbable forms and are given intramuscularly. Absorption of the steroid may be delayed either by adding an ester group or by injecting it in a microparticulate form.

The periods for which these drugs are likely to turn up in urine vary. ACTH disappears rapidly from the plasma in man, and does not appear in the urine. This same sequence of events presumably also occurs in the horse. The most detailed studies on the "clearance times" of corticosteroids in the horse were published by Chapman and his co-workers.[3] Using a radioimmunoassay (RIA) technique, these workers detected dexamethasone in urine for 155 hours after intramuscular (IM) administration of about 20 mg of a long-acting dexamethasone preparation. Similarly, depot preparations of flumethazone were detected for up to 90 hours after 10 mg doses IM. Most other steroid preparations tested by these workers were not detected for longer than about 48 hours. Racing chemists in the United States, however, generally use less sensitive thin layer chromatographic (TLC) screening techniques for the corticosteroids, and general experience in Kentucky suggests that corticosteroids rarely "show up" in TLC systems for more than 24 hours after dosing. Similarly, in one experiment where Chapman *et al.*[3] gave dexamethasone 21-sodium phosphate intra-articularly, it was detected in urine by RIA for only 24 hours, the same period for which it was detected after IM injection. On the other hand, however, Moss and Rylance[9] found prednisolone and its metabolites in equine urine for up to three days after its IM administration as the trimethylacetate. Of particular forensic interest was one instance in which excretion did not start for two days after the drug was administered and then continued for three more days which led to the suggestion that the drug had inadvertently been injected into fatty tissue which delayed both its absorption and excretion by 48 hours.

Unpublished observations by Horner and Moss[8] on the metabolism of dexamethasone in the horse showed that about 1% of an intravenous dose was excreted unchanged in the urine in the first 12 hours, with about 4% of the dose eliminated as the glucuronide or ethereal sulfate. In the first 24 hours, about 44% of the administered radioactivity was excreted, with a further 13% up to 60 hours. The same rate of excretion of radioactivity was seen after its intramuscular administration. After prednisolone administration in ponies, Moss and Rylance[9] reported detection of prednisolone and prednisone and their respective 11-deoxycortisol. Administration of prednisolone gave essentially the same metabolite pattern as did prednisone, with urinary excretion of the drug and its metabolites being complete within three days.

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