STEROIDAL ANTI-INFLAMMATORY AGENTS AND ADRENOCORTICOTROPIC HORMONE

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SUMMARY

The steroidal anti-inflammatory drugs are synthetic analogues of the natural anti-inflammatory hormone cortisol, whose metabolism in the horse is under the control of adrenocorticotropic hormone (ACTH). These corticosteroid analogues were developed to produce only the anti-inflammatory action of cortisol with little other physiological action. The mechanism of the anti-inflammatory action of corticosteroids involves protein synthesis; however, this action in the body is anti-anabolic and often results in tissue breakdown.

In equine therapeutic use, local administration is more common than systemic, as chronic systemic treatment can result in suppression of the immune response. In the horse the corticosteroids are injected locally to relieve bursa, tendon or joint inflammation. These agents inhibit the inflammatory response, but do not affect the source of the inflammation, and therefore the treatment is symptomatic only. Administration of corticosteroids requires close monitoring of the animal and it is recommended that the doses be minimal and infrequent.

Adverse reactions associated with equine corticosteroid therapy include septic arthritis, arthropathy and laminitis. The adverse reactions appear to be associated with the anti-anabolic effects, which lead to the suppression of the immune response. Systemic bacterial infections and delayed wound healing also may occur. Additionally, prolonged administration of corticosteroids can lead to suppression of adrenal secretion of cortisol. One way to avoid this problem is to administer exogenous ACTH to stimulate the production of cortisol and therefore maintain the function of the adrenal gland.

INTRODUCTION

The corticosteroids are a group of drugs that are chemically derived from the natural anti-inflammatory and mineralocorticoid agents of the adrenal cortex. By the early 1930s crude extracts of the adrenal glands were being used in human medicine and the

purification and characterization of these hormones were under way. Over the next 40 years these hormones were classified into three main groups and many powerful synthetic analogs of the prototype steroids in each group were developed. The adrenal corticosteroids in use in human and equine medicine today are classified into three groups, the anti-inflammatory or glucocorticoid agents, the mineralocorticoid agents and the adrenal sex hormones. The glucocorticoid or anti-inflammatory hormones are of major concern to us in equine sports medicine (Tobin 1981).

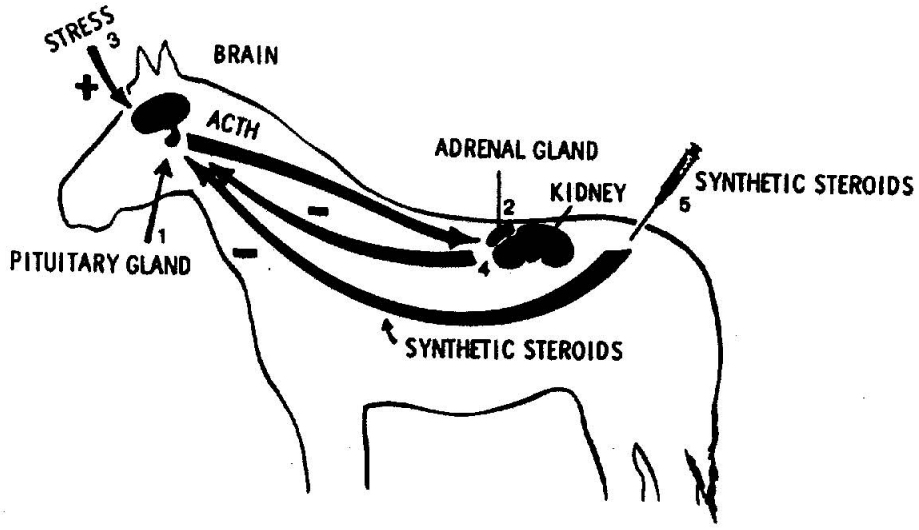


Figure 1: Control of plasma corticosteroid levels in the horse.

Adrenocorticotrophic hormone (ACTH) is secreted by the pituitary gland (1) and travels in the blood to the adrenal, where it regulates the activity of this gland (2). Various forms of stress (3) can increase the rate of release of ACTH and thus the activity of the adrenal gland (4) or administered by injection (5) act to inhibit the release of ACTH by a feed-back inhibition mechanism. Administration of prolonged high levels of steroid (5) can lead to atrophy of the adrenal gland by suppressing the release of ACTH. Abrupt cessation of steroid therapy can then lead to a corticosteroid withdrawal crisis and possibly death of the animal. Reproduced with permission from Charles C. Thomas, publisher.

PHARMACOLOGY

Cortisol and corticosterone are the natural anti-inflammatory steroids of equine blood, and their rate of secretion in the normal horse is thought to be about 0.5 mg/kg/day (Tobin and Nugent 1980). Their synthesis and secretion is under the direct control of adrenocorticotropic hormone (ACTH) (Figure 1). Both of these agents have anti-inflammatory actions, but they also have substantial effects on sodium and water retention, ie. they also have significant mineralocorticoid action. In an effort to accentuate the anti-inflammatory actions of the corticosteroids, a large number of analogues of cortisol have been developed which have greater anti-inflammatory actions and fewer mineralocorticoid actions (Table 1) (Tobin 1979). This approach has been very successful, and synthetic anti-

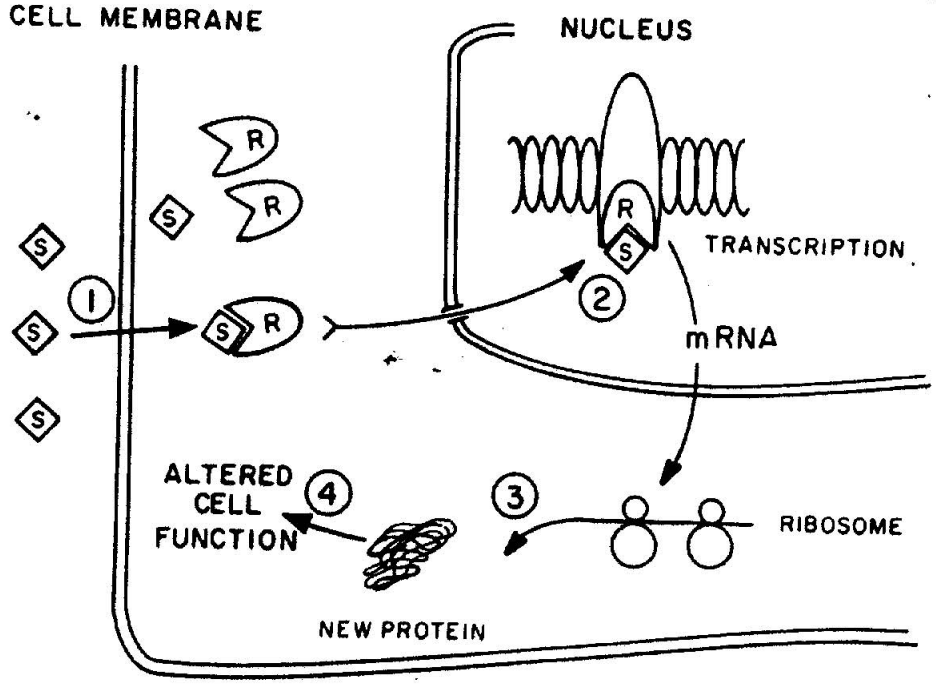


Figure 2:

Mechanism of action of the corticosteroids. Corticosteroid drugs (S) enter the target cells and bind to specific receptors (R) in the cell cytoplasm (1). In binding, they change the shape of these receptors and the altered drug-receptor complex diffuses into the nucleus of the cell. In the nucleus this complex binds to receptors on the genes and initiates transcription (2). The newly formed mRNA diffuses out of the nucleus, binds to the ribosomes and gives rise to new proteins which re-direct the function of the cell (4). Although the primary action of the corticosteroids is therefore to cause the synthesis of new proteins, their ultimate effects usually lead to tissue breakdown. Reproduced with permission from *J. Equine Med. Surg.*

inflammatory corticosteroids are available with up to 700 times more anti-inflammatory action than the parent cortisol with essentially no mineralocorticoid action. These agents are therefore primarily anti-inflammatory drugs, with relatively few actions on other physiological processes.

TABLE 1
RELATIVE POTENCY OF CORTICOSTEROIDS

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

The precise mechanism of the anti-inflammatory actions of the corticosteroids is not known, but it appears to involve the synthesis of new protein (Figure 2) (O'Malley and Butler 1977). After formation or injection, the corticosteroids travel through the blood, or tissue fluids when locally injected, to the cells where they are to produce their effects.

They then enter the individual cells and bind to specific receptor proteins in the cell. This corticosteroid-receptor complex then travels to the nucleus of the cell where it interacts with the DNA and gives rise to the synthesis of new protein. However, despite the fact that the actions of the corticosteroids requires the synthesis of new protein, their primary pharmacological actions appear to be anti-anabolic. As a rule these drugs lead to inhibition of cell growth, and to breakdown of cells, the effects of which are seen after local or systemic administration. Thus, although the initial action of this group of drugs is the synthesis of new protein, the results of this new protein synthesis is generally tissue breakdown and cell death. If one was to choose one word to describe the basic tissue level actions of the anti-inflammatory corticosteroids, the word would be anti-anabolic.

The systemic actions of the corticosteroids are well characterized. In horses and other species glucocorticoid administration leads to an increased breakdown of protein and lipid, which gives rise to an increase in liver glycogen and blood sugar, hence the name glucocorticoids. In the blood, glucocorticoids increase the packed cell volume and polymorphs, and reduce eosinophils (Figure 3), lymphocytes and basophils (Vernimb *et al* 1977). The effect on the destruction of lymphatic tissue is marked, and leads to their use in the therapy of lymphoma. The hemogram is characteristic and is sometimes called the glucocorticoid hemogram (Tobin 1981).

As might be expected based on their anti-anabolic effect, the glucocorticoids suppress growth and cause osteoporosis, which may lead to compression fractures.

They also produce a mood elevation in humans, which action has on occasion led to the abuse of this particular group of drugs for their mood elevating effects. These mood altering effects presumably also occur in animals.

THERAPEUTIC USE

Systemic corticosteroid therapy is less commonly used in equine sports medicine than local anti-inflammatory therapy. Nevertheless, the principles covering the systemic use of these agents are well understood. In general, one can administer a single large dose of a glucocorticoid to a healthy animal without any serious adverse effects. Prolonged treatment with corticosteroids can be dangerous, however, because it suppresses the

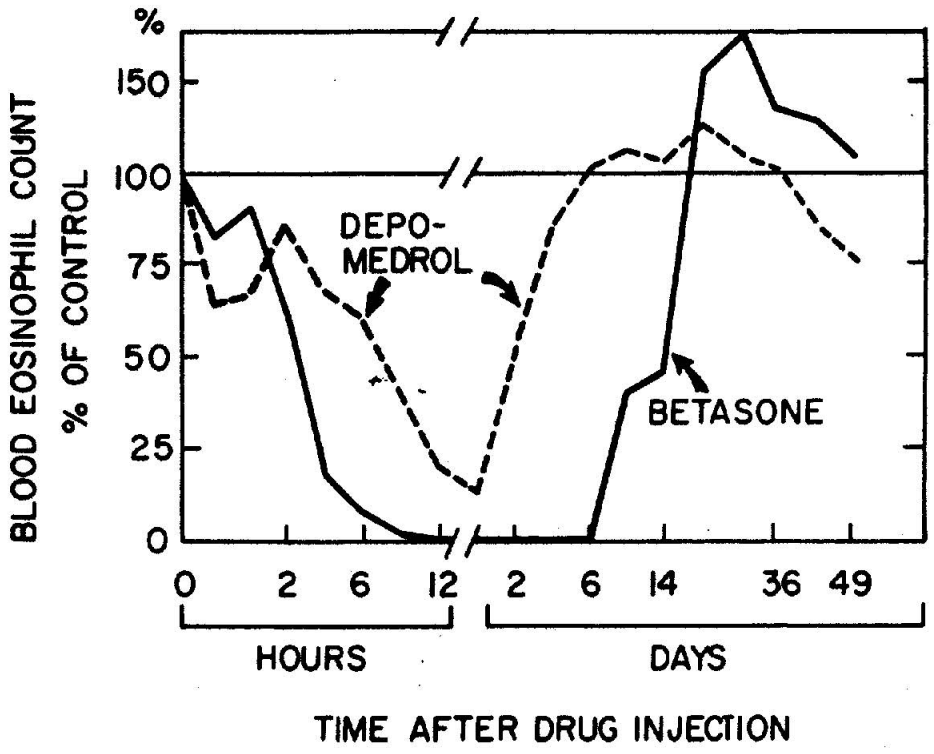
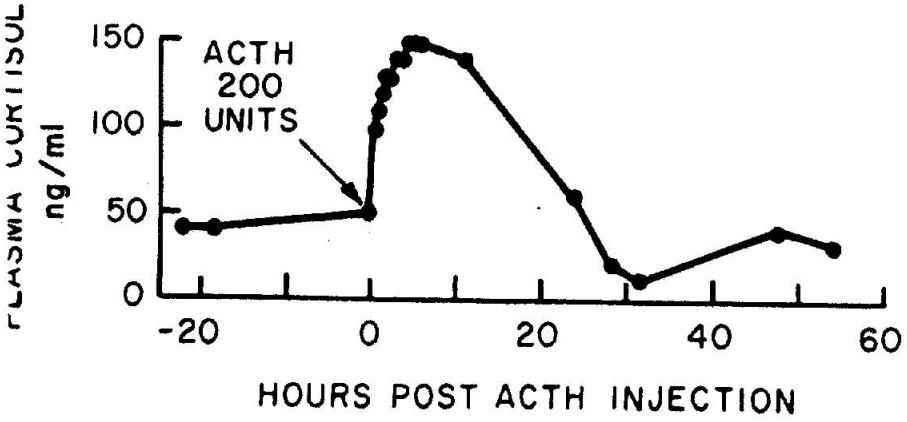


Figure 3:
Effect of bethamethasone phosphate/diproprionate and dimethylprednisolone acetate on blood eosinophil counts. Three mares were injected intra-articularly with 25 mg of betamethasone diproprionate and 10 mg of bethamethasone phosphate, while three other mares were injected with 40 mg of methylprednisolone acetate. The solid and dotted lines show the average eosinophil count for each group, respectively. The bethamethasone diproprionate/betamethasone phosphate combination of a soluble and long-acting steroid gave a more rapid onset combined with a longer duration of action. Reproduced with permission from Charles C. Thomas, publisher.

immune response, thereby increasing the body's susceptibility to infection and suppressing the adrenal cortex. For these reasons short term therapy with corticosteroids is much easier to justify than long term systemic treatment.

The glucocorticoids also produce their anti-inflammatory effects when injected locally. Because the anti-inflammatory effects of the corticosteroids are strongly expressed at the site of injection, local injection of the drug is an important use of this group of agents in equine sports medicine. The common local inflammatory responses seen in equine athletes therefore respond well to corticosteroid injection. Examples of such conditions include bursa, tendon, and joint problems, which are often restricted to specific areas and which respond well to injections of anti-inflammatory corticosteroid drugs given locally.

Whether injected locally or systemically the anti-inflammatory corticosteroids have the ability to suppress or eliminate the redness, heat, swelling, pain, and loss of function that characterizes the inflammatory response. At the microscopic level they inhibit the early and late signs of the inflammatory response. Capillary dilation does not occur, edema or fluid formation does not develop and the migration of inflammatory cells is inhibited. If these processes are under way, they are reversed and the tissue apparently returns to normal. They also inhibit the later stages of the inflammatory response such as capillary proliferation and scar tissue formation. The precise mechanism of these effects is not understood, but it is clear that the corticosteroids produce these effects quite independently of the agent that triggered the inflammatory response. The effect therefore appears to be a suppression of the inflammatory response rather than any direct neutralization of the cause of the inflammatory response. Because treatment with a corticosteroid merely suppresses the inflammatory response and does not affect the primary cause of the disease, treatment with these agents is symptomatic only and in no way affects the primary cause of the disease. This suppression of the clinical signs of disease is both the principal benefit of the use of corticosteroids and the most dangerous aspect of the use of these drugs in horses.



igure 4:

ffect of ACTH on plasma cortisol in the horse. Horses were injected with 200 units of CTH at the indicated times. The solid circles (●-●) show plasma levels of cortisol prior to id after IM injection of this drug. Reproduced with permission from *J. Equine Med. Surg.*

It has been said, with justification, in human medicine that the use of corticosteroids will allow a patient to walk all the way to the post mortem room, and the same holds true in equine medicine. For example, a horse with a corticosteroid injected joint will initially appear to be much improved and to "go sound". In point of fact, however, the condition may well progress at about the same rate as in the absence of the corticosteroid, and may, in fact, under some circumstances progress more rapidly than in the absence of corticosteroid treatment (Meagher 1970). Because the steroids are in essence anti-anabolic and suppress the ability of joint cartilage to repair itself, a horse with a corticosteroid treated joint may in fact wear its joint surface right down to the bone running on the corticosteroid injected joint.

After local injection of corticosteroids the ultimate success of this therapeutic approach depends largely on the amount of stress to which the treated area is exposed post-injection. For best results, the treated area should be rested to allow as complete healing as possible with as little scar tissue formation as possible around the joint. As a general rule the bursal injections of corticosteroids can be used with a minimum of post-injection rest and injection of the cunean tendon bursa (jacks), the trochanteric bursa (whorlbone) and the bicipital bursa can be made and the horse continued in racing. Similarly, bog spavins in young animals especially due to trauma rather than poor conformation, will respond well to the injection of corticosteroids.

Injection of corticosteroids into inflamed joints needs greater care in the selection of patient, technique of injection and post-injection care and support of the patient than is the case for tendon or bursal injections (McKay and Milne 1976). In keeping with the rule that corticosteroids cannot affect the basic cause of the inflammation, the joint should first be examined radiographically and, depending on the circumstances, bacteriologically for primary causes such as bacterial infections or mechanical causes of joint problems. As with any disease process, correction of the underlying problem greatly improves the prognosis and the eventual outcome of therapy.

Joint conditions that are particularly amenable to treatment with corticosteroids include non-traumatic arthritis, osteoarthritis uncomplicated by joint deformities, and traumatic arthritis without fractures or derangement of the joint. On the other hand, if the condition is chronic or there is osteoporosis present, the prognosis is much less favourable. Steroid therapy is contraindicated where there is erosion of the joint cartilage and in septic arthritis. This is because damaged or degenerated joint cartilage responds very poorly to steroid injection, and useful regeneration of the joint cartilage rarely occurs.

ADVERSE REACTIONS

Adverse reactions to the intra-articular injection of corticosteroids includes post-injection flare up, which commonly appears within hours of the intra-articular injection. The cause of this condition is unclear and the condition is usually mild and transient. Septic arthritis may be caused by the inadvertent introduction of septic material into the joint during the injection process. To avoid this, injections into joints should be made under strict aseptic conditions, and many practitioners routinely inject gentamicin into the joint cavity when introducting anti-inflammatory steroids.

Steroid arthropathy is the most important of the possible outcomes of joint injection with anti-inflammatory steroids. When steroid arthropathy occurs there is narrowing of the joint space, loss of articular cartilage, crepitation of the joint and osseous metaplasia or the formation of new bone around the joint. Steroid arthropathy appears to be the direct outcome of the anti-anabolic action of the steroids giving rise to suppression of growth of articular cartilage (loss of joint space), crepitation (friction of bone on bone with loss of

articular cartilage), with only the generation of new bone around the joint not being clearly related to the anti-anabolic actions of this group of drugs.

The role and use of intra-articular injections of corticosteroids in racing horses is the subject of much debate. When handled judiciously and in combination with rest, corticosteroids can be used to prolong the racing career of certain horses. The operative rule is that the corticosteroids should be used at minimum doses and as infrequently as possible. On the other hand with repeated joint injections, and particularly if the animal is not adequately rested, severe destruction of the joint will occur.

The adverse reactions to the corticosteroids appear to be related to their anti-anabolic effects. In the first place they suppress the immune response and many of their adverse reactions are linked to these effects. If horses are maintained on large doses of glucocorticoids for two weeks or more the suppression of the immune system leaves the animal open to systemic infections and also leads to feedback atrophy of the adrenal cortex. If the steroids are abruptly withdrawn, the animal may go into an Addisonian crisis. One way to handle this problem is to administer the steroids intermittently, whereas a second way is to administer exogeneous ACTH to maintain the adrenal cortex.

Other adverse reactions to the glucocorticoids include delayed wound healing, the reactivation of bacterial or viral disease, an increased incidence of cleft palate in the newborn and peculiar to the horse, the development of laminitis.

ACTH THERAPY

One way in which the actions of the corticosteroids can be mimicked is to administer ACTH to the horse to stimulate the release of adrenal glucocorticoids. Administration of this hormone brings about a prompt release of plasma cortisol which is equivalent to the systemic injection of corticosteroids (Figure 4). For example, in some classic experiments by James (1970) the administration of ACTH to ponies resulted in a prompt increase of plasma cortisol levels from about 50 ng/ml pre-injection to a peak level of about 150 ng/ml at about five hours after injection of the drug.

The duration of the effect of ACTH injection depends on the form in which it is injected, and in these experiments plasma cortisol levels had returned to control levels within about 24 hours of the treatment.

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