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CLINICAL USE AND CHARACTERISTICS OF THE CORTICOSTEROIDS

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Synthetic analogs of natural corticosteroids possess potent anti-inflammatory activity and are commonly injected intra-articularly for local relief of inflammatory lesions in performance horses. In addition to relief of inflammation and pain, corticosteroids are also anti-anabolic, which can delay healing of injured tissue. Although the anti-inflammatory effects of corticosteroids are therapeutically beneficial, the anti-anabolic effect is less beneficial. A joint with inflammatory changes and/or structural damage may regain racing soundness following intra-articular injection of corticosteroids, and the horse may return to useful competition. However, the suppression of anabolic activity in the joint may lead to an increased rate of joint breakdown.

The duration and effectiveness of corticosteroid therapy vary with the type of preparation used, severity of the inflammation, and the number of corticosteroid treatments previously administered. Complications associated with intra-articular corticosteroid therapy include septic arthritis, which is usually due to inadvertent joint contamination at the time of corticosteroid injection, and steroid arthropathy, which is characterized by an accelerated rate of joint destruction

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and radiographic evidence of severe degenerative joint disease. Prognosis for both of these conditions is poor.

Intra-articular corticosteroids are contraindicated in the presence of infection, structural damage, and instability in the joint, and when previous injections were ineffective. Aseptic technique is essential. Sufficient time for rest is required for proper healing to occur. Surgery should not be performed within 8 weeks following corticosteroid therapy. Adverse effects of systemic corticosteroid therapy include suppression of the hypothalamic-pituitary-adrenal system, increased susceptibility to infection, and laminitis. However, moderate use of glucocorticoids does not permanently affect adrenal function.

BACKGROUND

The corticosteroids are a group of drugs chemically classified as steroids that were originally identified in the adrenal cortex. By the 1930s, crude extracts of the adrenal cortex were being used in human medicine. During the following 60 years, many of the natural corticosteroids were identified and characterized. The most important steroids for veterinary practitioners are the glucocorticosteroids (glucocorticoids), which predominantly affect protein, fat, and carbohydrate metabolism and which also produce the powerful anti-inflammatory effects characteristic of this group of drugs. Cortisol is the principal naturally occurring glucocorticoid, but much more potent and specific synthetic analogues have been developed.

The second group of corticosteroids is the mineralocorticoid group, of which aldosterone is the classic example. Mineralocorticoids are responsible for sodium and water retention. The third group is the adrenal sex hormones. Of these three groups, the glucocorticoids, with their potent anti-inflammatory actions, are of major therapeutic importance to veterinarians and horsemen. It is this group with which this article is largely concerned.

GENERAL PHARMACOLOGY

Cortisol (hydrocortisone) and cortisone are among the natural anti-inflammatory corticosteroids, but they also have substantial effects on sodium and water retention. Based on early clinical observations suggesting anti-inflammatory actions of this group of agents, cortisone was tested in rheumatoid arthritis as soon as it became available, and it proved to be dramatically effective. A result of this work was the awarding of the Nobel Prize to Drs. Kendall, Reichstein, and Hench, the scientists who synthesized cortisone and directed its therapeutic application.

The pharmacologic effects of the corticosteroids are widespread and primarily concerned with adapting the organism to its environment. The glucocorticoids affect protein, carbohydrate, and lipid balance, whereas the mineralocorticoids affect water and electrolyte balance. The glucocorticoids have a permissive effect on many aspects of carbohydrate and lipid metabolism. In the absence of the adrenal cortex, survival is possible, but only under very rigidly prescribed conditions. The presence of adrenal hormones enables the animal to resist many types of adverse circumstances and greatly improves the survivability of the organism.

Because of the central importance of the corticosteroids in the adaptation of mammalian organisms to their environment, many drug companies have selec-

tively modified the basic glucocorticoid molecule to develop glucocorticoid analogs with more anti-inflammatory activity and less effect on water and salt retention. The basic steroid molecule is a four-ring structure (Fig. 1). Chemical alterations in the structure of cortisol changes the relative biological effects. For example, adding a double bond between C_1 and C_2 (as with prednisolone) improves glucocorticoid activity and reduces mineralocorticoid activity. Methylation at C_6 (as with methylprednisolone) further augments those effects (Fig. 1). This line of research has been very successful and has produced synthetic corticosteroids with 700 times more anti-inflammatory action than cortisol.

MECHANISM OF ACTION

The anti-inflammatory actions of the glucocorticoids appear to involve the specific receptor proteins in cells and the synthesis of new proteins. In vivo, corticosteroids travel to the effector cell and bind to a protein receptor in the cytoplasm of the cell. Then this receptor-steroid complex travels to the nucleus, where it binds with chromatin and, ultimately, directs the synthesis of new proteins. The initial action of all steroid hormones is therefore thought to be new protein synthesis, although these proteins may ultimately direct cellular breakdown and death of cells. The synthetic corticosteroids produce these effects locally when injected locally, and over the whole animal when injected systemically.

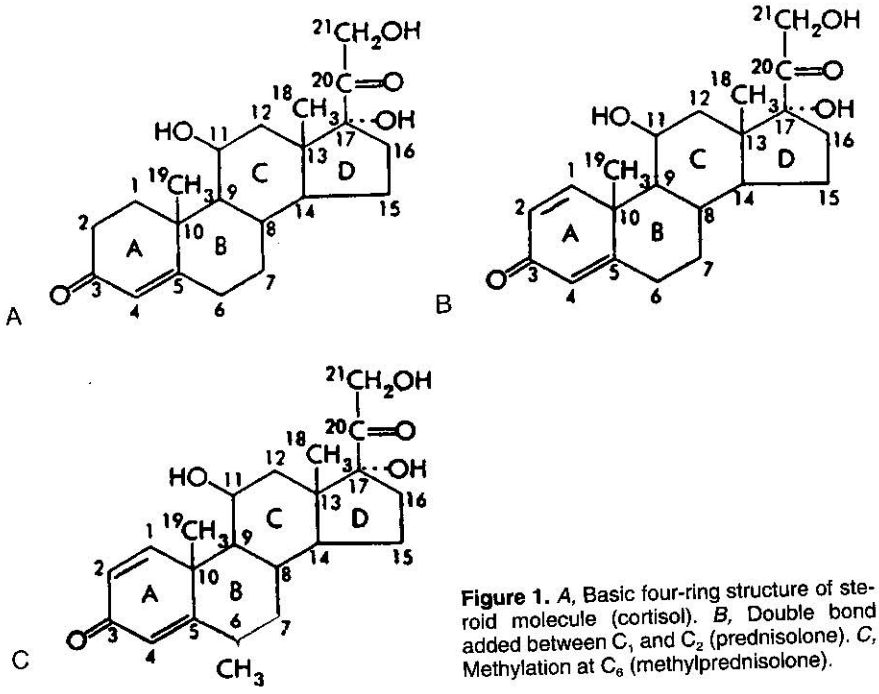

Figure 1. *A*, Basic four-ring structure of steroid molecule (cortisol). *B*, Double bond added between C_1 and C_2 (prednisolone). *C*, Methylation at C_6 (methylprednisolone).

EFFECTS ON INTERMEDIARY METABOLISM

The actions of the anti-inflammatory glucocorticoids can be described by one word: anti-anabolic. The anti-inflammatory actions of these agents are associated with a profound suppression of the immune response. Additionally, in actions that have proved impossible to separate from their anti-inflammatory effects, the glucocorticoids have equally potent effects on protein and carbohydrate metabolism.

The net effect of glucocorticoids on carbohydrate metabolism is gluconeogenic (i.e., they cause hyperglycemia at the expense of stored carbohydrate, protein, and fat). In addition to an increase in blood glucose, the glucocorticoids reduce peripheral utilization of glucose and increase liver stores of glycogen.

At least part of the gluconeogenic effect of the corticosteroids is due to their ability to mobilize amino acids from a number of tissues. These catabolic actions of the glucocorticoids eventually result in reduced muscle mass, reduced bone mass (osteoporosis), thinning of the skin, loss of hair, and negative nitrogen balance. The amino acids recovered from these tissues travel to the liver, where they are resynthesized into glucose for blood sugar and liver glycogen stores. Other effects from prolonged use are suppression of growth in younger animals, suppression of immune status, and suppression of the adrenal cortex.[38]

In humans, prolonged glucocorticoid treatment dramatically redistributes body fat. Fatty deposits on the back (buffalo hump) and face (moon face) and a loss of fat in the extremities lead to a very typical appearance characteristic of excessive corticosteroid use. Similar changes in lipid metabolism also likely occur in the horse, but these physical changes have not yet been detailed in this species.

The anti-anabolic effects of the glucocorticoids show up most clearly in children treated during their growth periods. Even small doses of glucocorticoids can markedly suppress the growth of children, and their eventual stature can be considerably less than in the absence of steroid therapy.

LOCAL ANTI-INFLAMMATORY EFFECTS

The anti-inflammatory effects of the glucocorticoids are quite localized after local administration of these agents. Because racehorses develop local areas of inflammation from conformational faults and the strains and stresses of racing, the ability of local corticosteroid injections to specifically and effectively suppress local inflammatory responses has led to widespread use of these drugs in equine sports medicine.[39,41]

Because of the marked reduction of pain and inflammation provided by these drugs, corticosteroids are widely used in the treatment of numerous equine musculoskeletal problems.[38] Many horses have competed successfully because of the relief gained from corticosteroids.

When administered systemically, corticosteroids promptly suppress the heat, redness, pain, swelling, and loss of function associated with an inflammatory response. When given locally, they have the same effect, although the anti-inflammatory effects (and many of the anti-anabolic effects) are restricted to the local area. Local injections of these agents are commonly used in bursal, tendon, and joint problems, where the drug is administered in small doses directly into the inflamed area.

JOINT STRUCTURE AND FUNCTION

Synovial joints (Fig. 2) are composed of the joint capsule, ligaments, synovial membranes, synovial fluids, and articular cartilage. The joint capsule and liga-

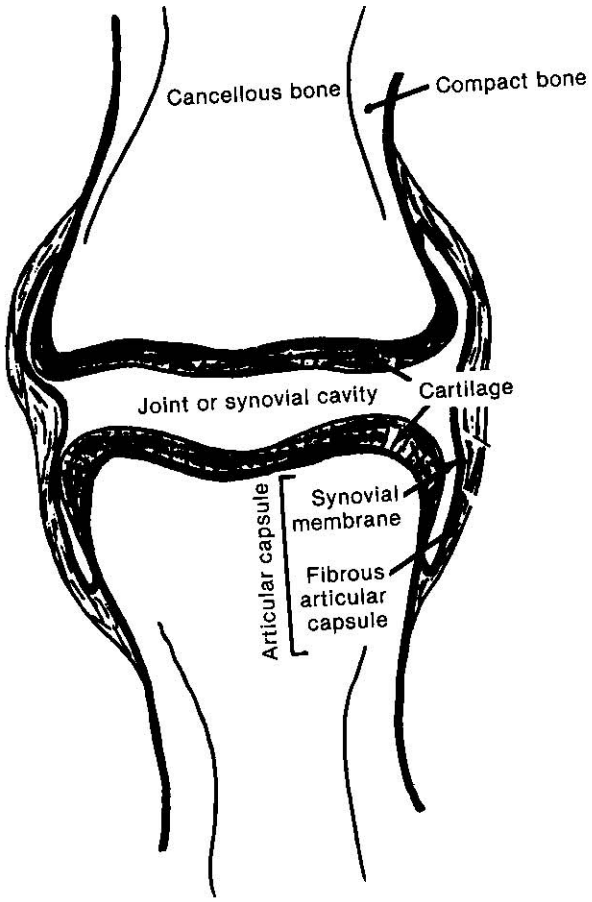

Figure 2. A normal synovial, diarthrodal joint. (*From* Sokolowski JH: Methylprednisolone acetate in the treatment of equine osteoarthritis. Equine Pract 4:17, 1982; with permission.)

ments form a sheath around the articular structures and are directly or indirectly attached to the bone. These structures are frequently continuous with the periosteum and serve to support the joint and limit its range of motion. Although the capsule and ligaments are predominately fibrous tissue and poorly vascularized, they contain numerous receptors for proprioception and pain. These pain receptors, along with the pain receptors of the periarticular soft tissues, are responsible for the pain of arthrosis.[27]

The inner layer of the synovial membrane is composed of connective tissue and two types of synoviocytes. Type A, the more common, are phagocytic and synthesize degradative enzymes, principally collagenases. Type B synoviocytes synthesize hyaluronic acid. The outer layer of the synovial membrane is fused with the joint capsule and connects to the periosteum and perichondrium. It is in this area that erosions and peri-articular osteophytes occur in degenerative joint disease.[27]

Synovial fluid is a dialysate of plasma that also contains synovial secretions, especially hyaluronic acid. Inflammation of the synovial membranes causes increased production and decreased absorption of synovial fluids resulting in excess fluid volume and distention of the joint capsule.[27] Hyaluronic acid gives joint fluid its viscous nature. In degenerative joint disease, both the concentration and degree of polymerization of hyaluronic acid are decreased, and these modifications reduce the viscosity of joint fluid.[46]

In synovial joints, a layer of hyaline cartilage covers the opposing surfaces of the articulating bones. Hyaline cartilage protects the bone from abrasion, dampens the forces of impact, disseminates the load, and facilitates movement between the articular surfaces.[40] Hyaline cartilage contains no nerve endings; therefore, the degree of articular damage correlates poorly with clinical pain.[46]

PATHOLOGY OF ARTHROSIS

The pathologic changes associated with degenerative joint disease are not completely understood but are thought to begin in the articular cartilage.[40] The hyaline surface experiences uneven overloading, which leads to altered lines of weight-bearing, deranged chondrocyte function, and reactive proliferation of chondrocytes. Chondrocyte injury further predisposes the cartilage to release of collagenases and other proteases, exacerbating matrix and cartilage breakdown. When arthrosis is present, there are increased intra-articular levels of collagenase, neutral proteases, and degradative products of proteoglycans. A secondary synovitis is produced, resulting in the release of inflammatory mediators from monocytes and macrophages.

Excessive joint loading creates altered stresses that derange normal chondrocyte function, leading to an imbalance between matrix mobilization and synthesis. Therefore, some areas of cartilage become softened and vulnerable to injury. Further degradation of the hyaline surface results in fissuring and flaking of the articular cartilage.[46]

The ability of articular cartilage to heal is limited. Repair is slow and easily disrupted by continuous degradative processes. After initial injury, there is an increase in chondrocyte mitotic activity and an increase in protein and glycosaminoglycan synthesis.[36] Despite these responses, surface defects are only partially corrected. Defects extending into the subchondral bone are invaded by granulation tissue, which eventually becomes fibrocartilage or imperfect hyaline cartilage.[52]

Considering the anatomy and physiology of diarthrodal joints and the pathology of arthrosis, the ideal drug for the treatment of degenerative joint disease would (1) promote synthesis of matrix components, (2) retard catabolic processes, (3) decrease inflammation of the synovium, (4) restore synovial fluid to normal, and (5) relieve pain.[46] No drug satisfies all of these objectives. However, intra-articular corticosteroids do retard catabolic (as well, unfortunately, as anabolic) processes, decrease inflammation of the synovium, and relieve pain.

ARTHROSIS IN RACING HORSES

Postmortem examination of Thoroughbred horses that were recently in training or racing reveal that a majority had at least subtle evidence of articular damage to the forelimb fetlock joints. Multifocal areas of chondrocyte degeneration and a reduction of proteoglycan are present in the superficial layers of the

articular cartilage. The loss of proteoglycan reduces cartilage resilience by decreasing the water-binding capacity of the tissue. This permits "wrinkling" of the cartilage along the plane of movement of the joint articulation.[51]

These postmortem lesions are frequently seen in both lame and sound racehorses; therefore, additional factors are probably involved in the progression of joint disease. Primary arthrosis in the horse is probably initiated by more than one factor, including (1) excessive work for immature, developing cartilage in younger horses, (2) lack of cushioning of the track surfaces, and/or (3) overuse of joints.[51]

Postmortem lesions seen in racehorses with mild fetlock lamenesses include slight soft-tissue swelling, joint fluid volume modestly increased but otherwise normal, and articular surfaces abraded with focal areas of dullness and fibrillation. The only radiographic evidence of disease may be equivocal narrowing of the joint space.[51]

Even though the gross appearance of the articular surface may not suggest disease, the synovial membrane, especially the part lining the palmar pouch, is frequently congested and hyperplastic. Often, the synovial tissues contain areas of lymphoid cells and macrophages, congested vessels, and edema. Pool et al[51] conclude that a low-grade synovitis and pain can be initiated by particulate matter and chemical irritants released from the damaged articular cartilage. This conclusion is supported by a study that created a painful synovitis from intraarticular injections of cartilage matrix particles.[20] Also, chondroitin sulfate, a major glycosaminoglycan of cartilage matrix, may activate the Hageman factor in vivo, which could activate the kinin pathway and trigger the chronic inflammatory response in the synovial lining of arthrotic joints. Furthermore, clinical observations show that joint lavage to remove cartilage debris relieves lameness for a few weeks until the accumulation of newly damaged cartilage triggers a new inflammatory cycle.[51]

In chronic arthrosis, additional joint deterioration may result in loss of much of the articular cartilage, sclerosis of subchondral bone, remodeling of articular margins, synovial abnormalities, bone production at ligamentous insertions, and joint instability.[51]

LOCAL EFFECTS OF GLUCOCORTICOIDS

Corticosteroids provide their anti-inflammatory effects by (1) stabilizing cellular lysosomal membranes, (2) reducing vascular permeability, (3) inhibiting leukocyte migration and decreasing their adherence to microvascular walls, (4) suppressing leukocyte superoxide production, (5) inhibiting platelet aggregation, and (6) reducing the inflammatory effects of the healing process that result in fibrosis.[1, 45] It has been suggested that the anti-inflammatory action of glucocorticoids is through the inhibition of the enzyme phospholipase A_2. When tissue inflammation occurs, arachidonic acid is released from the cell membrane phospholipid by the action of the membrane-bound enzyme, phospholipase A_2. Once arachidonic acid is released, it can serve as a substrate for two enzymes, cyclooxygenase and lipoxygenase. Through these two pathways, prostaglandins and thromboxane (cyclo-oxygenase pathway) and leukotrienes (lipoxygenase pathway) are formed. Reduction of these mediators of inflammation through phospholipase A_2 inhibition decreases the inflammatory response.[5] However, studies using dexamethasone (0.06 mg/kg)[31] and betamethasone (0.08 mg/kg)[32] to suppress these mediators of inflammation in equines have not supported the hypothesis that corticosteroids exert an anti-inflammatory action by inhibiting phospho-

lipase A_2. Further research is needed to elucidate the anti-inflammatory action of glucocorticoids.

The anti-inflammatory effects of corticosteroids are potentially useful to combat some of the effects of endotoxemia through (1) inhibition of phospholipase A_2 activity, which reduces eicosanoid production, (2) inhibition of tumor necrosis factor production by macrophages, (3) stabilization of cell membranes, and (4) prevention of neutrophil activation. However, the negative effects of the drug (including increased risk of laminitis, depressed immune responses, and decreased phagocytic activity of macrophages and neutrophils) preclude its routine use for endotoxemia therapy. Therefore, there is a need to develop other drugs for endotoxemia that do not possess the harmful side effects of glucocorticoids. The development of free radical spin-trap compounds has increased survival in laboratory animals receiving endotoxin lipopolysaccharide[7, 50] and holds promise for endotoxemia treatment in equines.

At the microscopic level, the corticosteroids act to inhibit both the early and late stages of the inflammatory process. In the early stages, the agents inhibit capillary dilation, fluid formation, and the migration of inflammatory cells from the blood into the damaged tissues. The drugs also inhibit the latter stages of inflammation, which include the formation of new capillaries and scar tissue. The precise mechanisms of these effects are not well understood, but it is clear that the corticosteroids produce these effects independent of the agent that elicits the response. This suggests that these drugs simply act to suppress the tissue response (the clinical signs) and in no way remove the primary cause. This effective suppression of clinical signs of disease is a potentially dangerous aspect of corticosteroid therapy. For example, a horse with structural damage in a joint injected with corticosteroids may regain racing soundness and return to useful competition. However, the suppression of anabolic activity in the joint may lead to an increased rate of joint breakdown. This aspect of the corticosteroids has given rise to the grim comment in human medicine that a patient on corticosteroids can "walk all the way to the autopsy room." Similarly, a horse running on a corticosteroid injected joint can completely erode the cartilage from the articular surfaces down to the bone.

INTRA-ARTICULAR CORTICOSTEROIDS AND JOINT STRUCTURE

To minimize systemic effects of glucocorticoids, the drugs are administered locally with intra-articular injections. However, the harmful effects of intra-articular corticosteroids were first realized within only a few years after this form of therapy began. In 1960, the term *steroid arthropathy* (to be discussed later) was introduced to describe this condition.[58]

Clinical experience is supported by scientific studies that show the detrimental effects of intra-synovial injections of corticosteroids on articular cartilage, including (1) decreases in cartilage elasticity and glycosaminoglycan content with progressive degeneration of the cartilage,[30, 37, 49] (2) formation of calcium deposits on the hyaline surface,[43] (3) thinning and fissuring of the cartilage,[41, 54] and (4) decreases in both viscosity and hyaluronic acid content of synovial fluid.[49] Furthermore, the severity of the lesions is proportional to the number of injections.[54]

In studies of induced arthritis,[6, 41, 61] corticosteroid therapy, before or after arthritis induction, significantly reduced joint capsule swelling, duration of lameness, and the time for return to normal thermographic patterns. Although clinical improvement is evident, at necropsy, corticosteroid-treated joints exhibit contin-

uing disease with gross pathology including thickened synovial membrane, plaque present on the synovial layer, and "ground-glass" appearance of the articular cartilage. It is concluded from clinical studies that although inter-articular corticosteroid therapy alleviates clinical signs of pain, total time required for healing is not decreased.[6]

In a review of clinical cases,[48] it was concluded that the combination of continued exercise and intra-articular corticosteroids in joints with prior osseous disease or instability caused steroid-induced arthropathies. It is possible that exercise alone could generate arthropathy in a joint with a traumatic lesion. However, it would be expected that the pain and inflammation from such a lesion would preclude the horse from stressing the joint sufficiently to cause severe degenerative changes.[49]

Experimentally created lesions in articular cartilage fill with fibrocartilage scar tissue, and, if the lesion is not too large and exercise is restricted, further damage will not occur.[36] However, lesions are larger and more severe in fractured joints injected with corticosteroids than in fractured joints alone (control).[41] Corticosteroids probably affect the generation of arthropathies in two ways: by delaying healing of the fracture, and by reducing synovial inflammation (which decreases the associated pain and permits strenuous exercise thereby exacerbating the osteoarthrosis).[49] Injecting a corticosteroid into a joint with a potentially repairable fracture accelerates joint degradation. By the time corticosteroids are no longer effective, the damage is usually too extensive for surgical correction.[41] Figure 3 is an example of a carpal joint with a slab fracture that was treated with

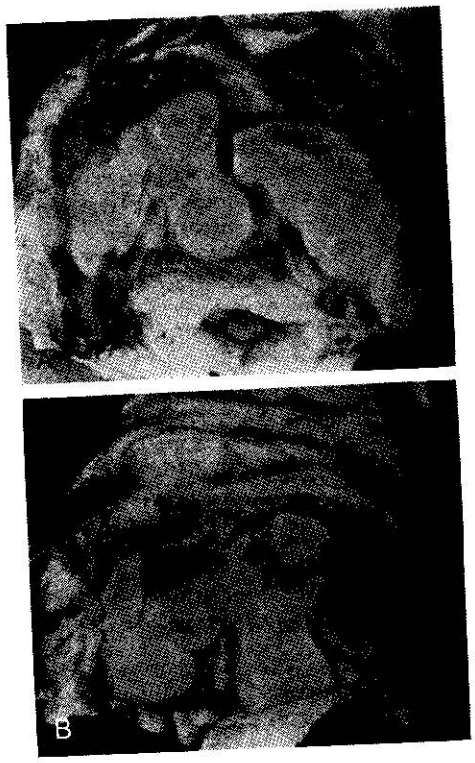

Figure 3. Proximal *(A)* and distal *(B)* rows of carpal bones in an intercarpal joint with a slab fracture (in distal row) treated with corticosteroids for 175 days. (*From* Owen Rhap R, Marsh JA, Hallett FR, et al: Intra-articular corticosteroid- and exercise-induced arthropathy in a horse. J Am Vet Med Assoc 184:302–308, 1984; with permission.)

intra-articular corticosteroids and subjected to strenuous exercise. There was complete erosion of the cartilage around the fracture, and the remaining cartilage was roughened and dull.

A study of intra-articular corticosteroid- and exercise-induced arthropathy in a horse[49] concluded that (1) normal doses of corticosteroids injected into a normal joint may not cause corticosteroid-induced arthropathy, even with strenuous exercise; (2) following corticosteroid injections, injured joints should be rested to allow the hyaluronic acid content to recover to normal concentration; and (3) even though hyaluronic acid concentration is increased during prolonged use of corticosteroids, the catabolic effects of corticosteroids on cartilage matrix will increase vulnerability of the articular cartilage. In that study, even the fractured joint retained reasonable integrity after corticosteroid injection and mild exercise. However, once exercise became intense, joint integrity declined rapidly. This finding supports clinical observations that fractured joints, inadvertently injected with corticosteroids, will heal if rested properly until there is radiographic evidence of bone healing.

The authors of one review of corticosteroid use in horses[51] related their experience with the development of "spontaneous" carpal chip fractures shortly after the joints were injected with corticosteroids for carpal lamenesses. They contend that pain relief following intra-articular therapy removed nature's protection against developing stress fractures that subsequently resulted in pathologic chip fractures.

Many studies showing adverse effects of corticosteroids administered the drugs at higher or more frequent dosages than routinely used.[9, 36, 37, 41, 49] In contrast, at least one study has shown a protective effect from lower doses of corticosteroids in horses.[26] In that study, the viscosity of synovial fluid increased following low-dose intra-articular corticosteroid therapy. Increased synovial fluid viscosity is also seen with higher doses of corticosteroids.[9]

In a study using clinically recommended dosages of corticosteroids, Trotter et al[60] injected three doses of methylprednisolone acetate (100 mg) into normal equine middle carpal joints at 2-week intervals. Horses were not exercised during the 8-week study. There was no lameness or joint swelling associated with the injections. Although the measured differences were not significant, all three radiograph examiners recorded joint-space narrowing in the injected joints. Clinically, this radiographic finding is associated with advanced joint disease, which was not the situation in these horses. The authors speculated that the degree of proteoglycan depletion found in the articular cartilage may have caused the physical deformation during weight-bearing. After 8 weeks, articular surfaces were free from any gross lesions. Microscopically, cartilage fibrillation was not present in any joint. Reduced matrix glycosaminoglycan content suggested a decrease in chondrocyte synthesis. In agreement with this study, proteoglycan content was decreased 50% in cartilage of horses 16 weeks after receiving only a single dose of methylprednisolone (120 mg) in a nondiseased metacarpophalangeal joint.[9]

In contrast, when horses received eight weekly injections of methylprednisolone (120 mg) in both carpal joints,[9] no visible damage was apparent, but cartilage in the injected joints sustained hypocellularity, empty lacunae, and decreased cell size.

GENERAL ADVERSE REACTIONS TO CORTICOSTEROIDS

It was noted earlier that glucocorticoids and mineralocorticoids both originate in the adrenal glands. It is important to remember that the naturally occurring glucocorticoids (e.g., cortisol and corticosterone) have mineralocorticoid activity as well. In therapeutic situations for osteoarthrosis, it is desirable for the

corticosteroid to have maximal anti-inflammatory activity and minimal adrenal suppression and mineralocorticoid effects.

There are undesirable side effects associated with glucocorticoid therapy. Foremost among these is suppression of the hypothalamic-pituitary-adrenal system, a life-threatening sequela.[17] It is difficult to completely eliminate the negative effects of glucocorticoid therapy, because all analogs of cortisol evoke this suppression to some degree.[21] Recovery time for hypothalamic-pituitary-adrenal inhibition is dependent on the length of treatment, potency of the glucocorticoid, and the extent of adrenal cortex atrophy.[8]

Adrenal insufficiency due to exogenous glucocorticoid therapy has been reported in the horse.[12, 14, 15, 24, 28, 47, 56, 59] In a clinical case of induced hyperadrenocorticism due to exogenous glucocorticoids,[12] a 10-year-old Quarter Horse was administered 12 mg triamcinolone acetonide by a local veterinarian. Three weeks later, the owner administered 200 mg triamcinolone. Seven days later, the owner administered a third treatment similar to the second. Two weeks later, the horse was admitted to a veterinary hospital for polyuria, signs of depression, and apparent weight loss. Initial blood work indicated a mild neutrophilia, lymphopenia, glucosuria, and elevations in aspartate transaminase (AST), gamma glutamyltransferase (GGT), and serum glucose. Cortisol concentration of 0 ug/dL suggested complete adrenal suppression and indicated the hyperglycemia was not due to excessive production of endogenous cortisol secondary to pituitary adenoma or hyperadrenocorticism.

High levels of GGT and AST and elevated concentrations of bile acids suggested hepatopathy. Ultrasonography of the liver revealed increased echogenicity of hepatic tissue. As no microorganisms were isolated from a percutaneous biopsy, the history and serum chemistry were consistent with a diagnosis of corticosteroid-induced hepatopathy. Six days after hospitalization, the horse became lame and exhibited signs of laminitis in the front feet. Repeat radiography of the front feet at 2-week intervals revealed increased ventral deviation of the third phalanges. Maintenance included extra-deep bedding and heart-bar shoes. The owner reported the horse's condition was stable 16 weeks after discharge.

Hyperadrenocorticism secondary to exogenous glucocorticoids is less common than hyperadrenocorticism due to an adenoma or hyperplasia of the pituitary gland.[3, 25, 34, 42] Polyuria and polydipsia result from osmotic diuresis (from hyperglycemia) and high glomerular filtration.[12] Hyperglycemia from excess glucocorticoids is caused by increased gluconeogenesis, decreased utilization of carbohydrates by the peripheral tissues, and increased utilization of free fatty acids from fat as an energy source.[11]

Glucocorticoid-induced neutrophilia is due to decreased margination of neutrophils in the vascular channels. This decreases diapedesis of neutrophils from blood vessels to tissue.[10] Induced lymphopenia is believed to result from decreased recirculation of lymphocytes into lymphoid tissue.[13]

Laminitis has been reported as a sequela to glucocorticoid use in horses.[12, 44, 63] A possible explanation of that phenomenon is that glucocorticoids potentiate vasoconstriction caused by catecholamines.[16] Digital vasoconstriction, resulting in decreased circulation to the laminae, is hypothesized as an important factor in the pathogenesis of laminitis.[33] Laminitis is more frequently associated with triamcinolone use than other corticosteroids.[38]

DURATION OF DRUG DETECTION AND DURATION OF PHARMACOLOGIC EFFECTS

Veterinarians routinely administer intra-articular injection of glucocorticoids to reduce the expense and minimize systemic side-effects of the drugs. However,

methylprednisolone is detectable in the plasma for at least 24 hours following intra-articular administration of methylprednisolone acetate (Depo-Medrol, Upjohn, Kalamazoo, MI) (Table 1). Methylprednisolone acetate and methylprednisolone have been reported to be detected in synovial fluid for 3 to 6 days and 5 to 36 days, respectively, following intra-articular injection. In the same study, intra-articular injection of methylprednisolone acetate produced adrenal suppression for approximately 4 days.[2]

Triamcinolone acetonide (Vetalog, Solvay, Mendota Heights, MN) has been detected in serum and synovial fluid for 1 to 3 days and 4 to 14 days, respectively (Table 1), following injection into three joints (6 mg/joint).[8] Because esterification of a corticosteroid with an acetonide purportedly decreases hydrolysis of a drug and prolongs the anti-inflammatory effect,[55] it is surprising that triamcinolone clears the joint this quickly. Adrenal suppression persisted for 5 days following intra-articular administration of triamcinolone.[8]

To assess the effects of dexamethasone (Azium, Schering, Omaha, NE) on adrenal suppression, horses received 0.044 mg/kg (Group 1) and 0.088 mg/kg (Group 2) intramuscularly every 5 days for six treatments. There was significant adrenal suppression in both groups the first day after treatment. However, on days 2 to 4, Group 2 horses demonstrated greater suppression than the group receiving the lower dose. There was no difference in ACTH-stimulation tests performed before the first injection and after the last injection, suggesting neither treatment regimen caused permanent detrimental effects on the adrenal cortex.[35]

A study of adrenal suppression in horses following single intramuscular doses of 0.044 mg/kg dexamethasone and 0.044 mg/kg triamcinolone acetonide revealed that both drugs exhibited maximal adrenal suppression by 12 hours postinjection. Serum cortisol was at pretreatment values by 7 days following dexamethasone administration; however, cortisol values did not return to pretreatment levels until 14 days after triamcinolone treatment.[56] Therefore, triamcinolone has a greater potential to induce iatrogenic hypoadrenalism than dexamethasone.

COMPLICATIONS OF INTRA-ARTICULAR STEROID THERAPY

Complications associated with intra-articular corticosteroid therapy include postinjection flare, osseous metaplasia, an increased risk of infectious arthritis, and steroid arthropathy in the treated joint.[22]

Table 1. CORTICOSTEROIDS APPROVED FOR INTRA-ARTICULAR USE IN THE HORSE

Compound	Relative Anti-inflammatory Potency	Concentration	Duration of Action
Cortisol	1	—	S
Methylprednisolone	5	40 mg/mL	L
Triamcinolone	5	6 mg/mL	I
Betamethasone	25	15 mg/mL	L
Isoflupredone	50	2 mg/mL	I
Flumethasone	700	0.5 mg/mL	S to I

S = short (8- to 12-hour biological half-life); I = intermediate (12- to 36-hour biological half-life); L = long (36- to 72-hour biological half-life).

Neither cortisone nor prednisone is suitable for intra-articular use because those drugs must be metabolized to cortisol and prednisolone, respectively, in the liver before they are active glucocorticoids.[57]

Postinjection flare

Some corticosteroids can cause an inflammatory response characterized by pain, swelling, and heat in the injected joint. The response begins a few hours after injection and can last for a few hours to several days. The reaction is probably a sterile inflammatory response induced by microcrystalline suspensions of the corticosteroid ester. The incidence of postinjection flare is approximately 2% and varies with the corticosteroid preparation used.[46] Clinical signs are usually mild and of short duration. Intra-articular injection of local anesthetics can be administered for relief of severe pain. Persistent pain may presage the development of septic arthritis.

Septic Arthritis

Septic arthritis usually occurs from inadvertent contamination of the joint during arthrocentesis but may result from hematogenous seeding of bacteria into a joint with compromised resistance to infection due to injected corticosteroids.[22] *Staphylococcus aureus* is the most common bacterium in corticosteroid-treated joints.[29] In a 9-day study of the effects of corticosteroids on synovial fluid parameters in infectious arthritis in horses,[61] moderate lameness was observed within 1 to 3 days following intra-articular injection of methylprednisolone (200 mg) and *S. aureus* bacteria. Appetite was depressed initially but returned to normal by 5 days postinjection. Periarticular swelling and edema of the distal limb developed 5 to 6 days postinjection. Rectal temperature increased with the onset of lameness (38.3 to 39.1 °C) and fluctuated throughout the experiment (38.4 to 38.9 °C).

Before injections, synovial fluid samples were pale yellow and clear, mucin precipitate quality was good, total protein concentration was less than 25 g/L, and mean white blood cell (WBC) count was normal ($0.067–0.156 \times 10^9$/L, predominantly mononuclear cells). In the infected joints, synovial fluid was turbid 4 to 24 hours after injection and contained flocculent debris, which increased in later samples. Color varied from yellow to orange to red. In most infected joints, mucin precipitate quality was poor or absent 1 day following infection. Reduced mucin precipitate quality is due to a decrease in the degree of polymerization of hyaluronic acid and interference with its synthesis.[53]

Total protein significantly increased in infected joints from a baseline of 25 g/L to 58 g/L on day 9.[61] The presence of corticosteroids in the infected joints significantly reduced the total protein response and delayed the onset of the protein rise. In control (treated with corticosteroid but uninfected) joints, total protein remained low, unlike WBC count, confirming its usefulness as an early indicator in the diagnosis of infection.

Synovial fluid pH values in the infected joints decreased significantly from an initial value of 7.32 to the lowest value of 6.30 3 days postinjection. Corticosteroids did not significantly affect pH. Therefore, synovial fluid pH is a good indicator of infection and should be included routinely in the synovial fluid analysis when the diagnosis of septic arthritis is in doubt.

In joints injected with *S. aureus* and corticosteroids, bacteria were detected in smears of 60% of the joints compared to 40% of joints injected with *S. aureus* alone.[62] Corticosteroids may interfere with the phagocytic action and lysosomal dissolution of synoviocytes and neutrophils, increasing the number of visible bacteria in a direct smear. Therefore, the detection of bacteria on smears of the synovial fluid is actually improved in the presence of corticosteroids.

A significant elevation in synovial WBC count coincided with the onset of

lameness 24 hours postinjection. However, at the onset of lameness, the WBC count was usually below the 'diagnostic' 50.0 × 10^9/L[38] for infectious arthritis. This is attributed to the inhibitory effect of corticosteroids on the migration of neutrophils.[23] Of additional importance from a diagnostic perspective, corticosteroid injection causes an initial rise in WBC count shortly after injection of noninfected (control) joints. Therefore, if corticosteroids are present in the lame joint, these two factors (inhibition of WBC rise and WBC rise following intra-articular injection) reduce the ability to make an early diagnosis of infection based on an elevated WBC count alone (Fig. 4). Corticosteroids have no significant effect on synovial WBC count after the infection is established. A marked increase in WBC count of almost 100.0 × 10^9/L is seen in the subsequent 24 hours. In infected joints, neutrophilia above 90% is a consistent finding. However, the presence of neutrophilia is not an adequate basis for diagnosis of infection because that phenomenon is caused by both corticosteroid injection and infection. Therefore, in corticosteroid-injected joints, total WBC count and neutrophil percentage are essential to diagnose infectious arthritis.[61]

Radiographic examination is of no value in the early stages of septic arthritis; however, radiographic signs may be dramatic in later stages of the disease.[22]

Experimental[61] and clinical[29] studies confirm that glucocorticoids have a masking effect on the detection of infectious arthritis. Most horses injected with *S. aureus* alone showed lameness within 24 hours, whereas horses injected with *S. aureus* and corticosteroids exhibited lameness 1 to 3 days postinjection.

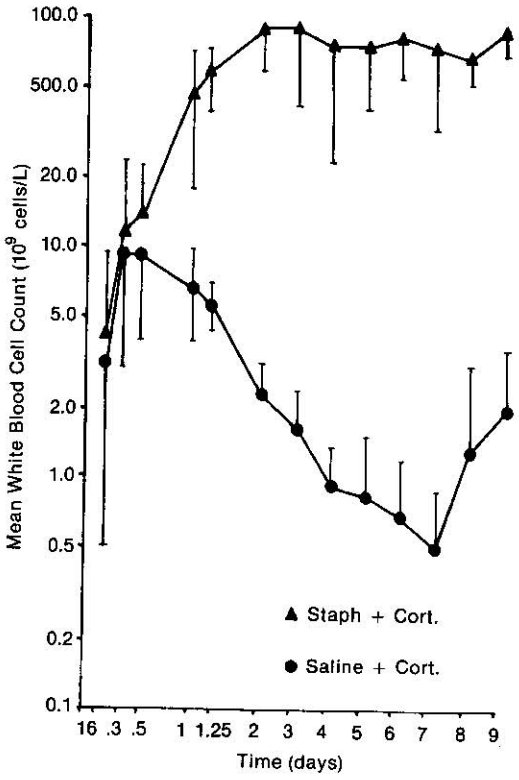

Figure 4. Comparison of synovial fluid white blood cell counts for *Staphylococcus aureus* and corticosteroid injected joints and saline and corticosteroid (control) injected joints. (*From* Tulamo RM, Bramlage LR, Gabel AA: The influence of corticosteroids on sequential clinical and synovial fluid parameters in joints with acute infectious arthritis in the horse. Equine Vet J 21:332–337, 1989; with permission.)

In conclusion, high and persistent absolute neutrophilia is one of the earliest diagnostic signs of post-corticosteroid-infected equine joints. The neutrophilia is delayed but not eliminated by the corticosteroids. Corticosteroids alone can also elicit a marked leukocyte response following the injection, but this will subside over 2 to 3 days rather than rise. A questionable or marginal total WBC count should be repeated within 12 hours to verify infection.

Treatment must be immediate and aggressive, including administration of systemic antibiotics, drainage and irrigation of the joint, and immobilization of the joint. Prognosis for soundness is usually grave.[22]

Osseous Metaplasia

Metaplastic bone formation results from inadvertent deposition of long-acting corticosteroids in the peri-articular soft tissues. The mechanism for this occurrence is unknown. Because short-acting corticosteroids do not cause the problem, it is assumed that the vehicle for the long-acting corticosteroids causes a reaction in the soft tissue. It may take several months for ossification to occur. The lesion may be quite large and result in mechanical interference with joint function. Surgical removal usually is not successful. Prevention is by avoiding inadvertent deposition of long-acting steroids in the peri-articular tissue.[22]

Steroid Arthropathy

Steroid arthropathy is characterized by an accelerated rate of joint destruction and radiographic evidence of severe degenerative joint disease (Fig. 5). Clinical signs include lameness, joint enlargement from both capsular distention

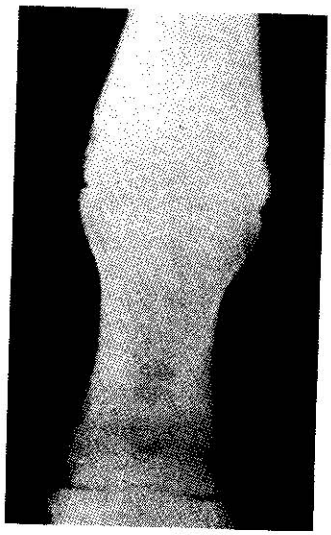

Figure 5. Anterioposterior radiograph of front fetlock with typical corticosteroid-induced arthropathy. Note diminished joint space and productive-destructive lesion on lateral aspect of joint. (*From* McKay AG, Milne FJ: Observations on the intra-articular use of corticosteroids in the racing Thoroughbred. J Am Vet Med Assoc 168:1039–1041, 1976; with permission.)

and osteophytic new bone growth, reduced range of motion, and crepitation. This disease results from intra-articular injection of equine joints that already have significant cartilage disease or are not rested properly following corticosteroid therapy.

A controlled study[49] showed the changes associated with corticosteroid use and continued exercise in racehorses. A 3-year-old Standardbred sustained a slab fracture of the third carpal bone. The horse was rested for the first 24 days, then resumed exercise for the next 127 days until severe lameness precluded further training. The intercarpal joints were injected with methylprednisolone (120 mg) 2 days after the injury and at 2-week intervals throughout the training period. Radiographic calcification of the periarticular soft tissue was first suspected on day 151. By day 159, there was considerable radiographic calcification typical of steroid-induced arthropathy (Fig. 6).

On necropsy, the synovial fluid was turbid and blood-tinged, the joint capsule was fibrotic, and the synovium was hyperplastic and hyperemic. The articular cartilage was completely eroded around the fracture line. Microscopically, the cartilage matrix at the border of the erosion was stained palely, suggesting a depletion of proteoglycan content, and lacunae were empty, suggesting chondrocyte death.

The opposite intercarpal joint, which was normal radiographically, was injected with the same dose and frequency (11 total injections) as the fractured joint. However, no evidence of corticosteroid-induced arthropathy developed in that joint. This supports the theory that corticosteroid-induced arthropathy develops in joints with prior osseous disease or instability.[48] There is no effective treatment for advanced steroid-induced arthropathy.[22]

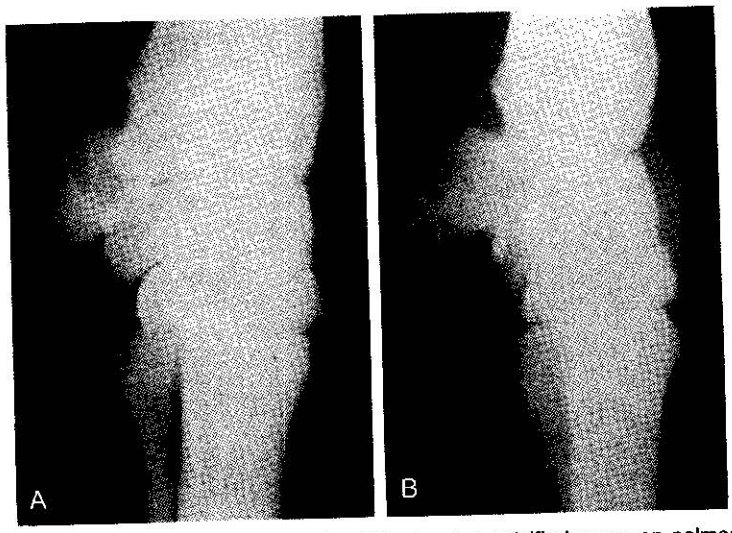

Figure 6. Lateral carpal views on *(A)* day 151, showing calcified areas on palmarolateral aspects of joint; and *(B)* day 159, revealing widespread calcification of soft tissue around joint. (*From* Owen Rhap R, Marsh JA, Hallett FR, et al: Intra-articular corticosteroid- and exercise-induced arthropathy in a horse. J Am Vet Med Assoc 184:302–308, 1984; with permission.)

CORTICOSTEROIDS AVAILABLE FOR INTRA-ARTICULAR INJECTION

The following corticosteroids are approved for intra-articular use in the horse.[4]

Triamcinolone acetonide (Vetalog, Parenteral, Solvay; triamcinolone acetonide injection, Fermenta). *Dose:* 6 to 18 mg depending on the size of the joint and severity of symptoms. Cases of laminitis have been reported following the administration of Vetalog. The mechanism of that response is not fully understood.

Isoflupredone acetate (Predef 2X, Upjohn). *Dose:* 5 to 20 mg, depending on the size of the joint.

Betamethasone acetate and Betamethasone sodium phosphate (Betavet Soluspan, Schering-Plough). *Dose:* 2.5 to 5 mL.

Methylprednisolone acetate (Depro-Medrol, Upjohn; methylprednisolone acetate injection, Fermenta). *Dose:* 40 to 240 mg, depending on the size of the joint.

Flumethasone (Flucort, Syntex). *Dose:* 1.25 to 2.5 mg daily.

CLINICAL GUIDELINES CONCERNING USE OF INTRA-ARTICULAR CORTICOSTEROIDS

Intra-articular corticosteroid use is contraindicated in the presence of infection,[46] structural damage, or instability in the joint,[19] and when previous injections have been ineffective.[46]

Aseptic technique is essential.

Corticosteroids slow the rate of healing of articular cartilage, joint capsule, ligaments, and bone. Therefore, a sufficient time for rest (30 days minimum) is essential while healing occurs.[18] Otherwise, degenerative changes will be more severe if intra-articular corticosteroid therapy is combined with continued exercise.[41]

Surgery should not be performed within 8 weeks following corticosteroid therapy.[41]

Moderate use of glucocorticoids does not permanently affect adrenal function.[35]

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