

# Myths and Truths About Controlling Pain and Inflammation in Horses

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## Introduction

The modern uses and common diseases of horses predispose them to conditions of pain and inflammation. Inflammation is common to all injured body tissues and the basic response is the same irrespective of the cause of the injury. The clinical signs associated with inflammation have been described in medical literature for thousands of years. Celsius, in the first century AD described the signs of inflammation as "redness and swelling with heat and pain". Virchow in the 19th century added "disturbed function" to the definition. While it may be difficult to appreciate redness in pigmented or hair covered skin, swelling with heat, pain and loss of function are easily recognized in inflammatory conditions in the horse. The demands of pleasure and competitive riding and racing result in many inflammatory conditions of the musculoskeletal system. The nature of the work that horses perform causes sprains and strains, and in some cases, failure of ligaments, tendons, joints and bone, which may lead to temporary or permanent disability. Common diseases of horses such as pneumonia/pleuritis and colic also involve inflammation.

Inflammation is a natural defence mechanism against tissue injury and usually leads to successful tissue healing. Sometimes, the inflammatory process itself actually causes further injury. In such circumstances it is appropriate to intervene with analgesic (pain-killing) and anti-inflammatory drugs. There are several categories of drugs that control pain and inflammation in horses. The non-steroidal anti-inflammatory drugs, corticosteroids, and chondroprotective drugs act predominantly at the site of injury to control inflammation and thereby control pain. Local anesthetic drugs work on pain receptors to alter the perception of pain without modifying inflammation.

### Arachidonic acid pathways

Inflammation is a primary cellular response to an insult or injury from bacteria or other infectious organisms, or chemical and physical agents. Arachidonic acid is a fatty acid component of the phospholipid membrane of cells. When the cell membrane is injured, the enzyme phospholipase A2 cleaves arachidonic acid from its position in the cell membrane. Once free of the cell membrane, arachidonic acid is further acted on by **cyclooxygenase** or **lipoyxygenase** enzymes. Cyclooxygenases are found in all cells except mature red blood cells. When cyclooxygenase acts on arachidonic acid, the end result is the formation of **prostaglandins**, **thromboxane** and **prostacyclin**. These chemicals have potent effects on the vascular system. By their opposite effects under normal circumstances, they provide a "check and balance" system that maintains normal blood vessel muscle tone. In inflammatory conditions, this balance is lost. Initially, the effect of prostacyclin predominates and causes increased blood flow to the damaged tissue from dilation of blood vessels. The increased blood flow increases the supply of nutrients, oxygen, antibodies, white blood cells and other defensive substances to the injured site. Swelling and heat results from the increased blood flow and from leaking of blood fluids into the surrounding tissues. Further on in the inflammatory process, thromboxane and prostaglandin activity dominates, resulting in widespread vasoconstriction, pain, fever, platelet clumping and formation of thrombi (blood clots), and reduced oxygen delivery to the tissues. Prostaglandins in the brain are responsible for raising the hypothalamus set point and causing fever.

Prostaglandins also have beneficial effects on kidney function, gastrointestinal and reproductive system functions and normal bone healing. In the kidney, local prostaglandins maintain renal blood flow and urine production. In the gastrointestinal tract, they inhibit gastric acid secretion and increase the secretion of protective gastric mucus. Loss of these protective prostaglandins, causes the horse to develop ulcers in the gastrointestinal tract. Prostaglandins also have major effects on the reproductive tract. They cause the corpus luteum to regress (the source of progesterone for maintaining pregnancy) and cause the uterus to contract, inducing labour or abortion. Prostaglandins are also involved in the formation of normal bone, so the administration of anti-prostaglandin drugs can delay fracture healing and decrease bone remodelling.

Alternatively to the cyclooxygenase pathway, arachidonic acid can be acted on by the lipoyxygenase enzyme, to produce the **leukotrienes**. Lipoyxygenases are located in white blood cells, platelets, and various cells in the lungs. The leukotrienes cause constriction of the airways, constriction of blood vessels, leaking of blood fluids from the blood vessels, and the formation of blood clots. They also attract additional circulating white blood cells to the area of inflammation.

## Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

The nonsteroidal anti-inflammatory drugs are among the most widely used drugs in veterinary medicine. Some NSAIDs have valuable therapeutic properties, and some have a great potential for toxicity. Due to their potential for misuse, a thorough knowledge of their clinical pharmacology is important for effective use.

### Pharmacology

The NSAIDs commonly used in horses are:

- aspirin
- phenylbutazone
- dipyrone
- flunixin meglumine
- meclofenamic acid
- ketoprofen

All NSAIDs are weak acids and highly bound to proteins in the blood. Therefore, they are well absorbed from the stomach, but then because of protein binding, most of the drug remains in the blood. Only low levels of NSAIDs are found in normal tissues and joint fluid. In damaged tissues and joints however, NSAID levels increase to therapeutic levels because of the increased blood flow and the leaking of blood fluids from damaged blood vessels.

### Mechanism of action

The NSAIDs block the cyclooxygenase enzyme, interrupting formation of thromboxane, prostacyclin and the prostaglandins from arachidonic acid. This results in antipyretic action (reduces fever), mild pain relief, anti-inflammatory effects and inhibition of platelet clumping. Recent research has also shown that some of the NSAIDs act on pain receptors in the central nervous system and block pain in the same way as drugs like morphine. NSAIDs are also thought to alter immune system responses and suppress inflammatory mediators other than the cyclooxygenase products.

### Drug interactions

The occurrence and potential hazards of drug interactions must be considered with therapeutic use of the NSAIDs. In general, any two NSAIDs administered together will be additive in their effect. Since all NSAIDs act by the same mechanism of cyclooxygenase inhibition, higher dose of a single NSAID should produce the same response.

Because all of the NSAID drugs are highly bound to blood proteins, caution must be used when other highly protein bound drugs are administered. Competition for protein binding sites can result in dramatic increases in free drug available for pharmacological action and cause toxicity.

Some of the effects of the diuretic, furosemide (Lasix®), are dependent on normal prostaglandin levels. Concurrent administration of furosemide and NSAIDs may reduce the efficacy of furosemide.

### Adverse effects

The adverse effects of the NSAIDs are related to blocking cyclooxygenase in tissues where prostaglandins are beneficial and protective. Reduction in protective prostaglandins results in constriction of blood vessels and tissue damage in the kidney and reduction in blood flow and protective mucus production in the gastrointestinal tract resulting in ulcers, colic and diarrhea. NSAIDs have a higher incidence of toxicity in foals because their kidney function is not fully developed. When it is necessary to use NSAIDs in foals, they should be administered at the lowest possible doses. NSAIDs should be administered very cautiously to dehydrated horses. Blood concentrations will be greater than normal in the dehydrated horse and are more likely to cause toxicity.

Treatment of NSAID toxicity is intensive and mainly supportive. The hypoproteinemia that results from loss of blood proteins into the ulcerated gastrointestinal tract can be corrected with intravenous infusions of plasma. Commercial sources of equine plasma are available, but this therapy is extremely expensive in adult horses. The fluid and electrolyte losses that accompany the diarrhea are managed with commercially available intravenous fluids. Broad-spectrum antibiotics are indicated when there is evidence of bacterial septicemia (blood infection). Colic pain must be managed with opioid analgesics, as additional NSAID therapy must be avoided. Anti-ulcer medications may be beneficial and speed recovery. Surgical removal of damaged sections of intestine may be necessary in some cases. Recovery is usually slow and in severe cases the prognosis is always guarded.

# Aspirin

## Pharmacology

Aspirin irreversibly binds to cyclooxygenase in platelets and other cells and prevents the conversion of arachidonic acid to prostaglandins, thromboxanes and prostacyclin. The action of most of the other NSAIDs on platelet cyclooxygenase is reversible, therefore, aspirin has the greatest anti-clotting activity of the NSAIDs. Aspirin is only available in oral formulations as boluses containing 60 or 240 grains of aspirin or as a powder. Aspirin is well absorbed from the stomach, and high concentrations are attained in the liver, heart, lungs, kidneys and blood. Aspirin is partially converted in the blood and by the liver to salicylic acid, and both are rapidly excreted by the kidneys into the urine. Salicylic acid is a natural component of horse urine, but the normal concentration is quite low. Drug testing for aspirin requires accounting for this natural production. Because of the irreversible binding to cyclooxygenase, the anti-coagulant activity of aspirin lasts far longer than its antipyretic (fever reducing), anti-inflammatory and analgesic (pain relieving) activity. A single dose of 20 mg/kg will prolong bleeding time in horses for 48 hours. Therefore, an anti-clotting aspirin dosage is 10 mg/kg every 2 to 3 days, or 20 mg/kg every 4 to 5 days.

## Uses/indications

Aspirin has the weakest anti-inflammatory and analgesic (pain relieving) activity of the NSAIDs in horses, so it is rarely used in horses for inflammatory conditions. Its anti-clotting action is useful in treating conditions in the horse that involve damage to blood vessels and the subsequent formation of blood clots, such as laminitis, verminous (parasite) colic, recurrent uveitis (periodic ophthalmia or "moon blindness"), and endotoxemia.

## Adverse effects

The most common adverse effect of aspirin therapy is stomach or intestinal irritation with blood loss. Because of its effect on blood clotting, aspirin therapy should be discontinued one week prior to the horse having any surgery. If used in pregnant mares, aspirin may delay foaling or increase bleeding at foaling.

# Phenylbutazone ("bute", PBZ)

## Pharmacology

Phenylbutazone (PBZ) has analgesic (pain relieving), anti-inflammatory, and antipyretic (fever reducing) activity from inhibition of cyclooxygenase. It is available in many intravenous and oral formulations (powder, paste, gel, tablets). The injectable formulation must be given by careful intravenous injection, otherwise it causes severe tissue damage if given intramuscularly or subcutaneously. Following oral administration, PBZ is well absorbed, but time it takes to reach peak blood levels is delayed by feeding the horse, as the PBZ sticks to feed particles. In the blood, greater than 99% of the PBZ is carried bound to blood proteins. Phenylbutazone is converted by the liver to oxyphenbutazone, a metabolite with the same action as PBZ, but removed slower from the body than PBZ. The capacity of the liver to process PBZ becomes overwhelmed at relatively low drug doses. Therefore, increasing doses of PBZ can easily result in toxicity. In the horse, the therapeutic effect of PBZ lasts for more than 24 hours, due to the slow excretion of the oxyphenbutazone metabolite. PBZ and oxyphenbutazone will cross the placenta and are excreted in mare's milk.

## Uses/indications

Phenylbutazone is used extensively in horses for a variety of common musculoskeletal disorders including navicular disease, laminitis, osteoarthritis and degenerative joint disease. It is economical and many brands are available. The use of PBZ in performance horses is very controversial, and it is highly regulated by individual performance associations. It is less effective in the therapy of colic and endotoxemia than flunixin meglumine (Banamine®). Phenylbutazone has less anti-clotting activity than aspirin and clinical use is not associated with increased bleeding. An initial dose of 4.4 mg/kg every 12 hours for the first day of therapy is followed by 2.2 mg/kg once a day for several days. Due to drug accumulation from the slow excretion of oxyphenbutazone, long-term PBZ therapy for chronic lameness conditions should be on an every other day basis with the lowest effective dose.

## Adverse effects

Gastrointestinal effects are the most important adverse effects of PBZ therapy in horses. Clinical signs include loss of appetite, depression, colic, weight loss, ventral edema, hypoproteinemia (low blood protein), and diarrhea. Hemorrhages and ulcers may occur in the mouth, esophagus, stomach, cecum and right dorsal colon. These toxic effects are related to the dose of PBZ given. Horses that receive less than 0.4 g/100 lbs of body weight per day for 4 days (4 grams to a 1000 lb horse) or 0.1-0.2 g/100 lbs of body weight per day for up to 50 days remain clinically normal. Horses that receive more than 0.4 g/100 lbs of body weight per day for 4 days develop toxicity. In a study, horses that received approximately 7 g of PBZ developed gastrointestinal ulcers within 24 hours. Ulcer formation is thought to be predominantly due to PBZ-induced blood vessel constriction to the mucosal lining of the gastrointestinal tract. PBZ also causes kidney damage from inhibiting the prostaglandins that maintain kidney blood flow. Because of its mechanism of action against prostaglandins, PBZ toxicity occurs whether the drug is administered intravenously or orally. Dehydration contributes to the toxicity potential of PBZ by reducing the blood flow to the kidney, therefore it is very important that horses on PBZ therapy have adequate

water intake.

Since normal liver function is required for conversion and elimination of PBZ and oxyphenbutazone, liver disease can result in toxicity even when PBZ is administered at recommended doses.

Because PBZ can alleviate lameness in horses for several days following therapy, it may be used to disguise lameness for the purpose of soundness examinations or for competitive purposes.

Chronic, low-dose PBZ has been given to broodmares with no obvious effect on their ability to conceive or carry a foal to term. However, its use should be kept to a minimum in pregnant mares.

PBZ may interact with other highly protein bound drugs such as phenytoin, warfarin, and other anti-inflammatory agents and result in toxicity. Protein bound drug is not available to tissues for pharmacological action. When a drug is 99% plasma protein bound, only 1% of drug is available to tissues for effect. If another highly protein bound drug is administered simultaneously, that has a greater affinity for the protein binding sites, a small change in the degree of protein binding will result in a dramatic change in drug available for action. This explains the well known interaction between warfarin (an anti-clotting treatment for navicular disease) and PBZ. With the administration of PBZ to a horse on warfarin therapy, the PBZ displaces some of the warfarin from protein binding sites. If the amount of protein binding of warfarin is reduced to 98%, then the concentration of free warfarin effectively doubles (to 2%) and can cause a bleeding crisis in the horse.

Phenylbutazone competes for the same cellular binding sites as thyroid hormone. Treating horses for just 5 days causes a significant decrease in baseline thyroid hormone (T3 and T4) concentrations. Treated horses have a greater than normal response to injection with thyroid stimulating hormone.

## **Dipyrone (Austin, Langford, P.V.L.)**

### **Pharmacology**

The pharmacology of dipyrone has not been well investigated in horses. Dipyrone is thought to act similarly to other NSAIDs by inhibiting cyclooxygenase. Dipyrone is available as a 50% solution (500 mg/ml), and can be administered IV, IM or SC to horses.

### **Uses/indications**

Dipyrone has analgesic (pain relieving), antipyretic (fever reducing), and slight anti-inflammatory properties. It reportedly has antispasmodic activity on bradykinin-induced spasms of the gastrointestinal tract (spasmodic colic), but does not have the potency of flunixin meglumine (Banamine™) for other types of colic. Dipyrone does not affect normal intestinal motility. Most veterinarians feel that other analgesic agents are more effective than dipyrone in the therapy of **equine** colic or pain.

### **Adverse effects**

High doses or chronic therapy with dipyrone may result in damage to the horse's bone marrow; manifested by abnormal blood cell production. Other adverse reactions include gastrointestinal upset, pain at the injection site, skin reactions, hemolytic anemia, tremors, and anaphylactic (allergic) reactions. It should not be administered to horses with blood or bone marrow problems. It should not be administered concurrently with acepromazine, phenylbutazone, or barbiturate anesthetics.

## **Flunixin Meglumine (Banamine®, Schering Plough Animal Health)**

**Pharmacology** - Flunixin meglumine is a very potent inhibitor of cyclooxygenase that is available in injectable, oral paste and oral granule formulations. Flunixin is rapidly absorbed following oral administration, and peak blood levels occur within 30 minutes. The onset of anti-inflammatory and analgesic action is within 2 hours and duration of action can be up to 36 hours. Like other NSAIDs, flunixin is highly protein bound. Flunixin is eliminated by the kidneys, and can be measured in urine for 48 hours after a single dose. Flunixin's pain relieving effect lasts long after the concentrations in the blood have become negligible. The long duration of pain relief appears to be due accumulation in inflamed tissues and to interaction of flunixin in the central nervous system with opioid receptors in a manner similar to morphine.

**Uses/indications** - Flunixin is used in horses for a variety of inflammatory and painful conditions: colic, colitis, exertional rhabdomyolysis ("tying up"), endotoxic shock, respiratory disease, eye injuries and diseases, general surgery, laminitis, and other musculoskeletal disorders. Extensive research substantiates the efficacy of flunixin over other NSAIDs in the therapy of endotoxic shock in horses. Flunixin may be used to prevent abortion in endotoxemic pregnant mares or after attempting to "crush" a twin. The recommended dose is 1.1 mg/kg of body weight once daily, but your veterinarian may need to increase the frequency of this dose in very painful conditions such as colic. Low dose therapy with flunixin, at one

quarter the label dose administered three to four times a day, has anti-endotoxic effects without masking signs of colic pain or causing toxicity. Conversely, extremely high doses of flunixin may mask signs of surgical colic pain and prevent the veterinarian from recognizing the need for surgical intervention. Flunixin does affect normal platelet function, but blood clotting failure is not seen with clinical use and administration prior to surgery is safe.

**Adverse effects** - Flunixin has similar adverse effects as PBZ, but appears somewhat less toxic than PBZ in horses. High doses can result in loss of appetite, depression, and gastrointestinal tract ulcers. In normal foals, the label dose of flunixin administered for 5 days did not produce adverse effects, but six times the label dose resulted in gastrointestinal ulcers. In another study, where foals were administered flunixin at the label dose for 30 days, all treated foals developed gastric ulcers. At three times the label dose given for 7 days, approximately 50% of normal horses or ponies will develop gastric ulcers.

Intramuscular injections of flunixin have been incriminated in cases of fatal clostridial myositis (bacterial infection of the muscle) in horses. When injected into muscle, the drug's formulation causes slight tissue damage and an anaerobic (without oxygen) environment. On rare occasions, a clostridial organism spore is picked up as the needle passes through the horse's haircoat and is injected into the tissue. In the anaerobic environment, the spore becomes activated and proliferates, releasing toxins and causing massive muscle damage. If not treated promptly and aggressively, clostridial myositis is rapidly fatal.

## **Meclofenamic Acid (Arquel®; Vetrepharm)**

### **Pharmacology**

Meclofenamic acid is a very palatable oral granule used in horses for the treatment of inflammatory musculoskeletal conditions. This drug has not been extensively researched in veterinary medicine. Feeding prior to dosing may delay absorption of meclofenamic acid from the horse's stomach.

### **Uses/indications**

Meclofenamic acid is dosed in horses at 2.2 mg/kg of body weight given as a 20 grams of Arquel® granules to a 1000 lb horse once a day in the feed. It is an unusual NSAID in that its anti-inflammatory and analgesic action can take 36-96 hours to develop. Clinical efficacy can be seen for days once therapy is discontinued. Repeated daily dosing does not result in drug accumulation, therefore this is a useful drug for chronic inflammatory conditions such as navicular disease or bone spavin. Many horses can be maintained comfortably with twice weekly dosing without side effects. In clinical studies, researchers found clinical improvement in the lameness of 2/3 of treated horses, but found it difficult to predict which horses would respond to meclofenamic acid.

### **Adverse effects**

At normal doses, some decrease in blood protein concentrations may be seen. Doses of 68 times the label dose result in toxicity, including mouth ulcers, loss of appetite, depression, edema and weight loss. When administered at the label dose chronically to stallions and pregnant mares, no toxic effects were seen.

## **Ketoprofen (Anafen®; Rhone Merieux, Canada Inc)**

### **Pharmacology**

Ketoprofen is a propionic acid NSAID. Initial work suggested that ketoprofen had an inhibitory action on lipoxigenase in addition to cyclooxygenase inhibition. However, clinical work in horses and other species has shown that ketoprofen only blocks the production of cyclooxygenase derived mediators of inflammation. Ketoprofen and its active metabolites persist in inflamed tissues at concentrations higher than blood concentrations, so the anti-inflammatory effects of ketoprofen are not related to its concentration in the blood. Ketoprofen is rapidly eliminated from the blood, therefore kidney-damaging drug accumulation does not occur. The maximum anti-inflammatory effects of ketoprofen occur at 12 hours after a dose and last for 24 hours. Ketoprofen is available as 100 mg/ml solution for intravenous injection at a dose of 1 mg/kg.

### **Uses/indications**

Advantages claimed for the use of ketoprofen in horses include inhibition of bradykinin and inhibition of both cyclooxygenase and lipoxigenase pathways. This anti-lipoxigenase effect is seen in laboratory studies, but has not been demonstrated in actual studies in live horses. A cartilage-protective effect that has been seen in cartilage cultures in the laboratory has also not been demonstrated in live horses. It is recommended for musculoskeletal injuries, where a single dose gives good pain relief and anti-inflammatory activity for 24 hours.

### **Adverse effects**

Ketoprofen does not appear to be substantially different from flunixin meglumine for clinical use in horses, but appears to be less likely to cause gastrointestinal ulcers than other NSAIDs. In a small toxicity study in horses, ketoprofen produced fewer gastrointestinal lesions than treatment with flunixin meglumine or phenylbutazone. At doses many times the label

dose, clinical signs of ketoprofen toxicity are similar to those seen with other NSAID toxicities.

## Corticosteroids

### Pharmacology

Cortisol and corticosterone are the natural body corticosteroids produced by the adrenal glands. The adrenal glands are very small, but very important glands that lie on top of the kidneys. They are stimulated to produce corticosteroids by adrenocorticotropic hormone (ACTH) released by the anterior pituitary gland in the brain. Release of ACTH from the pituitary gland is influenced by factors including exercise, stress, surgery, cold exposure, and hypoglycemia. The major control of ACTH release is feedback inhibition by high blood levels of corticosteroids. This occurs with the natural release of corticosteroids from the adrenal glands, or from the administration of a corticosteroid drug formulation. After release from the adrenal glands, corticosteroids circulate in the bloodstream until they reach cellular targets. At the level of individual cells, corticosteroids enter the cell and bind to specific protein receptors. The corticosteroid-protein complex then enters the cell nucleus and alters the cell's production of proteins. Changes in protein production result in altered cellular function, this can have a wide variety of effects in the horse's body, depending on the type of cell involved.

The natural function of corticosteroids is to protect the supply of blood glucose critical for normal brain function. They increase blood glucose concentration by counteracting the effect of insulin and by mobilizing fatty acids and amino acids from body stores for additional glucose production by the liver. Therefore, corticosteroids have a breakdown (catabolic) effect on body muscle and fat stores, but can cause excessive fat to accumulate in the liver. The elevated blood glucose concentration often improves the horse's mood and behavior and improves appetite. Corticosteroids also effect body water regulation, commonly causing excessive drinking/excessive urination (known as polyuria/polydipsia or PU/PD). Corticosteroids predispose horses to gastrointestinal ulcers as they increase the secretion of gastric acids and alter protective gastric mucus. This action is synergistic with NSAIDs, and the risk of gastrointestinal ulcers dramatically increases when both types of drugs are used together.

The corticosteroids have potent anti-inflammatory activity. They stimulate the cellular production of *lipocortin*, which inhibits phospholipase A2, the enzyme responsible for cleaving arachadonic acid from damaged cell walls. Therefore the corticosteroids inhibit both the *lipoxxygenase* and *cyclooxygenase* pathways of inflammation, blocking formation the leukotrienes as well as prostaglandins, prostacyclin, thromboxane, In addition to blocking the inflammatory mediators, the corticosteroids suppress white blood cell functions and antibody production. This is reflected in alterations in the numbers of white blood cells circulating in the bloodstream and the white blood cell response to injured and infected tissues. In acute inflammation, the corticosteroids maintain the integrity of the blood vessels and reduce edema formation, and limit the movement of white blood cells into injured tissues. In later stages of wound healing, corticosteroids reduce the proliferation of blood vessels and connective tissue, which decreases scar tissue production and slows wound healing.

There are many corticosteroid preparations available for veterinary use. They are commonly referred to collectively as "steroids" or "cortisone". Differences in chemical structure of these drugs determine the potency of anti-inflammatory activity, duration of effect, and duration of suppression ACTH release from the brain. The corticosteroids can be classified by comparing them to hydrocortisone, which is identical to cortisol, the natural corticoid hormone.

### Drug Duration Comparative of Action Potency\*

Hydrocortisone 8-12 hrs 1  
Prednisone 12-36 hrs 4  
Methylprednisone 12-36 hrs 5  
Triamcinolone 12-36 hrs 5  
Isoflupredone 12-36 hrs 50  
Dexamethasone 32-48 hrs 30  
Betamethasone 32-48 hrs 30  
Flumethasone >48 hrs 120

\* Potency is determined by comparison to a cortisol a value of 1.0.

### Uses/indications

Corticosteroid therapy is directed at modifying the body's response to inflammation; it is not directed at treating the underlying disease process. Therefore, the veterinarian will use the smallest dose that achieves the desired effect in order to limit adverse side effects. Generally, anti-inflammatory doses are 10 times the physiological levels, doses to suppress the immune system are twice the anti-inflammatory dose, and doses to treat shock are 5 to 10 times the immunosuppressive dose. Product formulations have differences in onset and duration of action. Phosphate and succinate

esters are very water soluble and have a rapid onset of action. They are usually used intravenously in the management of shock, especially due to trauma. Commonly administered products include:

- methylprednisolone sodium succinate (Solu-Medrol®; Pharmacia and Upjohn, Inc)
- prednisolone sodium succinate (Solu-Delta-Cortef®; Pharmacia and Upjohn, Inc)
- dexamethasone sodium phosphate (Aziium SP®; Schering-Plough Animal Health).

Shock type doses must be high, which would require administering many bottles of these drugs to an adult horse. Because of the expense, this treatment is not common in horses.

Solutions of free steroid alcohols are administered intravenously or intramuscularly and their use is usually limited to acute, but not immediately life-threatening conditions such as chronic obstructive pulmonary disease (heaves) attacks, snake bites, vaccine reactions, and insect bite hypersensitivity. Examples include.

- dexamethasone (Aziium®; Schering-Plough Animal Health)
- flumethasone (Flucort®; Syntex Animal Health, Inc).

Acetate and acetonide esters are given intramuscularly, subcutaneously or intra-articular (into the joint) for a prolonged effect. Absorption of drug into the systemic bloodstream occurs slowly, over days to weeks. Examples of long-acting formulations include:

- methylprednisolone acetate (Depo-Medrol®; Pharmacia and Upjohn)
- triamcinolone acetonide (Vetalog®, Ciba-Geigy, Inc)
- isoflupredone acetate (Predef 2X; Pharmacia and Upjohn)
- betamethasone dipropionate (Betasone®; Schering-Plough Animal Health)

These long-acting corticosteroids always depress normal adrenal gland production of cortisol when given systemically, but this effect is minimal when they are administered directly into a joint. The immune system suppressive action of the long acting formulations make the horse more susceptible to bacterial, viral and fungal diseases. Intra-articular corticosteroids should not be given if infection is present, or if there is detectable structural damage or instability in the joint. Sterile injection technique is essential. Sufficient rest time must be given while healing occurs, otherwise continued exercise will result in severe joint damage. Surgery should not be performed on corticosteroid-injected joints for two months following injection or poor healing may result.

Oral corticosteroid formulations are well absorbed and can be administered to horses. **Prednisone** and **prednisolone** tablets are the most commonly prescribed products and are frequently administered for long-term therapy of adrenal gland insufficiency (hypoadrenocorticism) or immune-mediated diseases such as chronic obstructive pulmonary disease (heaves), inflammatory bowel disease, and chronic inflammatory skin diseases (*Culicoides* hypersensitivity). Prednisone is metabolized by the liver to prednisolone; therefore prednisolone is preferred in horses with liver disease.

Corticosteroids are usually administered at the lowest dose known to be effective. If long term medication is not necessary, the drug can be discontinued abruptly with relatively few adverse effects such as adrenal gland suppression. For long term therapy, corticosteroid doses should be given at the lowest possible dose and if possible, should be administered orally, on an every other day basis. After long term therapy, horses must be "weaned off" corticosteroids by giving progressively smaller doses of corticosteroids over the course of several weeks to allow the adrenal glands to resume their normal function. If corticosteroid therapy is stopped abruptly, the sudden lack of circulating steroids can cause severe problems in many body systems.

### **Adverse effects**

A major concern with administration of corticosteroids to horses is the risk of inducing laminitis (founder). This occurs sporadically and can not be scientifically demonstrated with all corticosteroid products. However, the consequences of laminitis can be so devastating, that it is a consideration with administration of any corticosteroid product to horses. Scientific studies have shown that corticosteroids can cause constriction of arteries of the feet of normal horses. In another study, high doses of corticosteroids alone did not induce laminitis. But when the same horses were fed carbohydrate overload diets after corticosteroid treatment, the resulting laminitis was more severe than in horses that did not receive corticosteroids.

Local injections of corticosteroids into joints or tendons can relieve pain and inflammation and return normal function. However, if the underlying damage is not corrected, continued use of the damaged joint will only cause further deterioration. Injected joints initially show less pain and swelling than non-injected joints, however production of normal

bone and cartilage stops and normal joint lubricating substances are reduced. Continued mechanical trauma results in wearing of joint surfaces, loss of joint function, and can ultimately lead to permanent disability of the horse.

Intra-articular corticosteroid injections also increase the risk of bacterial infection in the joint. The action of the corticosteroid reduces the joint's resistance to bacterial infection, and the suppression of an inflammatory response makes it difficult to detect that an infection is present. The treatment of a joint infection must be prompt and aggressive, and may include systemic antibiotics, and drainage and flushing of the affected joint. Prognosis for soundness is grave.

Intra-articular injections can result in post-injection flare, an inflammatory response characterized by pain, heat and swelling in the injected joint. The response is seen within a few hours of injection and can last several days. This response is a reaction to the formulation of the corticosteroid. The incidence of post-injection flare is about 2% and varies with the product administered. Post-injection flare is difficult to distinguish clinically from life-threatening bacterial infection.

Because of immunosuppressive effects, corticosteroid therapy is associated with an increased risk of bacterial, viral and fungal infections. This effect is dose-dependent and unlikely to occur with a single dose of a short-acting corticosteroid.

Corticosteroid therapy can cause gastrointestinal ulceration. This toxicity is compounded when corticosteroids are administered along with NSAIDs.

## **Topical Capsaicin (Equi-Block®, Equi-Block DT®, Equi-Tite®; EquiFlite Technologies Inc.)**

**Capsaicin** is the active chemical in hot chili peppers. Application to a nerve fiber stimulates the release of **substance P**, the chemical responsible for transmitting the nervous signal for pain (eg, that burning sensation when you eat a jalapeno pepper). Repeated applications of capsaicin depletes the nerve's stores of substance P, and halts the transmission of the pain signal. Capsaicin ointments have been available as a topical cream for the treatment of painful diabetic nerve disorders in people. The human ointments contain 0.075% capsaicin.

A line of equine products containing capsaicin have been developed and aggressively marketed (Equi-Block®, Equi-Block DT®, and Equi-Tite®). Despite advertising claims, there are no scientific studies that document that these products are useful for the control of pain in horses. While the Equi-Block contains 0.2% capsaicin, there is no evidence that this concentration is adequate to penetrate horse skin (which is much thicker than human skin). EquiBlock DT is indicated for daily therapy, and contains 0.02% capsaicin. The Equi-Tite formulation is indicated as a liniment and contains only 0.012% capsaicin.

As these products are not sold as drugs, there is no requirement that the manufacturer must prove that they actually work. If the capsaicin is absorbed sufficiently to deplete stores of substance P and block the pain sensation, there is still no affect on the original cause of the horse's pain. Therefore, this is very similar to using a local anesthetic block on a lame horse, and could result in severe damage from the horse using an unsound limb because it does not feel pain. In addition, the initial use of capsaicin in people is associated with a painful burning and tingling sensation and can cause serious skin reactions. Care should be taken in applying these products to horses.

**Chondroprotective Drugs** - The chondroprotective drugs are used to prevent or slow the progression of degenerative joint disease (DJD, "arthritis"), rather than simply reduce the clinical signs of pain like the anti-inflammatory drugs. Chondroprotective drugs help the normal activity of chondrocytes (the cells in cartilage) and prevent or reduce damage to the joint cartilage from enzymes and other inflammatory mediators such as prostaglandins.

**Hyaluronan (Hyalovet® 20; Vetrepharm  
Hylartil® Vet; Pharmacia and Upjohn  
Hyonate®; Bayer Inc  
Hy-50® Mylan; Bexco  
Synacid®; Schering-Plough Animal Health)**

Hyaluronan (HA), formerly known as hyaluronic acid, is a normal component of joint cartilage and fluid. It has been widely used as a treatment for joint diseases of people and horses.

### **Pharmacology**

Hyaluronan is chemically known as a non-sulfated glycosaminoglycan (contains no sulfur molecules). It is produced by the membrane that lines the joint capsule and disperses into the joint fluid and taken up by the joint cartilage. HA provides joint lubrication and protection of the joint cartilage from shear and compressive forces as the horse moves. It also reduces prostaglandin concentrations and scavenges free radicals in inflamed joints.

Hyaluronan is primarily used in the treatment of degenerative joint disease (traumatic arthritis) of the carpal (knee), fetlock,

coffin and hock joints of performance horses. Although cartilage damage is not always directly responsible for the horse's lameness, it is the limiting factor in rehabilitation of arthritic joints in the horse. It appears that HA concentration in joint fluid is reduced in degenerative joint disease. Injecting additional HA directly into the joint appears to normalize the joint fluid and increase the production of HA by the joint membrane.

The actual injected HA remains in the joint for only a few hours, but its effect on the joint appears to last days to months. It does not appear that HA has any direct effect on joint cartilage.

### **Uses/indications**

Clinical reports generally support the use of hyaluronan in the treatment of equine joint disease for reducing inflammation and lameness. In performance horses, a rapid return to work is a desirable outcome, and the action of HA has been considered a natural treatment without the risk of adverse effects associated with other treatments. Hyaluronan is effective for mild to moderate degenerative joint disease. For horses with severe DJD, HA therapy alone is not adequate return them to athletic function.

The commercially available hyaluronan products for horses vary in the molecular weight of the HA they include. There is considerable scientific controversy over the relationship between the molecular weight of the HA product and the effectiveness of treatment in equine joint disease. While some studies indicate that the high molecular weight products are superior, this has not been completely demonstrated in clinical trials. In addition, the cost of the lower molecular weight products is considerably less than the high molecular weight products.

A formulation of HA for intravenous use has recently been approved in the United States and Canada (Hyonate®, Bayer Inc.). This formulation provides a more convenient route of administration, allows for treatment of joints following injection of local anesthetic drugs without delay, and may reduce the adverse effects of intra-articular injections (bacterial infection, mechanical damage, drug-induced inflammatory reaction within the joint). It is not known how intravenously administered HA achieves therapeutic levels in the joint, but in a controlled study, horses treated with intravenously administered HA had a reduced degree of lameness compared to untreated horses.

Intra-articular HA can be used in combination with other intra-articular medications such as corticosteroids. The combination therapy can result in a better and longer lasting improvement in lameness than either product alone.

## **Polysulfated Glycosaminoglycans (Adequan®; Luitipold Pharmaceutical, Inc.)**

### **Pharmacology**

Adequan® is **polysulfated glycosaminoglycan** (PSGAG), made from an extract of cow lung and trachea that is then sulfated. The result is a large, charged molecule composed of galactosamine, glucosamine, and hexuronic acid. After administration, PSGAG binds to cartilage components. The precise mechanism of action of PSGAG in joints is unknown, but there are many studies demonstrating a beneficial effect of this product on damaged joints. Currently, PSGAG is thought to decrease destructive enzymes, act as an anti-inflammatory agent and stimulate the normal production of hyaluronan and glycosaminoglycan.

### **Uses/indications**

Adequan® is indicated for the treatment of degenerative joint diseases. It is available in two formulations, one for intra-articular injection and one for intramuscular injection. When injecting directly into the joint, one 250 mg vial is used once a week for five weeks. When using the intramuscular injection, 500 mg is injected every four days for four weeks.

"Maintenance" therapy is not addressed by the manufacturer and has not been investigated in scientific studies, but veterinary practitioners have administered additional doses at intervals of weekly or monthly intervals with success in some horses.

When performing the intra-articular injection, the area to be injected must be clipped and cleansed as if performing a surgical procedure. Intra-articular injection should not be made where the skin has been blistered or is scurfed. Intramuscular injection of Adequan® can be performed in the same manner as any other intramuscular injection.

### **Adverse effects**

Polysulfated glycosaminoglycan is related to the anti-clotting drug, heparin, and has some similar effects on blood clotting in horses. Although bleeding tendencies have been seen in people, prolonged administration of PSGAG in horses and dogs does not cause clinically apparent bleeding problems.

Severe inflammation after intra-articular injection of Adequan® can occur due to the individual horse's sensitivity to the drug, traumatic injection technique or from exceeding the recommended dose, frequency or number of injections. This inflammatory reaction can occur within 48 hours of injection, and is characterized by increased lameness, and heat, pain and swelling of the injected joint. This inflammatory reaction can be treated with non-steroidal anti-inflammatory drugs cold

water therapy and rest, and usually resolves in a few days.

The most serious side effect of intra-articular Adequan® injection is joint infection, usually from skin bacteria deposited into the joint from the needle tip. The anti-inflammatory action of PSGAG increases the ability of a few bacteria to successfully infect the joint. Joint infection can be life-threatening. Successful treatment of an infected joint requires prompt identification and aggressive antibiotic treatment. Unfortunately, the early signs of an infected joint are indistinguishable from the signs of the non-infectious joint inflammation due to AdequanB injection. Giving NSAIDs for joint inflammation will mask the signs of infection and further delay recognition that the joint is infected. Because of the potential for joint inflammation and infection from direct injection of the joint, many veterinary practitioners prefer the intramuscular product.

**Chondroitin sulfates/Glucosamines (Cosequin®; Nutramax Laboratories Flex Free®; Vita-Flex Nutrition Co. Inc. Xtra-Flex®; MVP Glyco-flex®; Vetri-Science Laboratories)**

These chondroprotective products are sold as nutritional supplements - "nutriceuticals". The classification of nutraceutical means that these products are not considered as "drugs" and do not have to meet the same standards of purity, efficacy and safety that the Bureau of Veterinary Drugs would require of a drug for the treatment of degenerative joint disease. The nutraceuticals are promoted as oral supplements supplying the horse with the "building blocks" necessary for repair of damaged cartilage. However, the building blocks for production of joint cartilage are adequately supplied by most normal equine diets. There are many anecdotal reports of improvement in clinical signs of lameness in horses supplemented with nutraceuticals. However, well-designed scientific studies proving that these products are effective have not been published. Some of the nutraceutical manufacturers are sponsoring such studies and results are pending. These products appear to be safe, may improve a lameness condition, but are somewhat expensive for long-term therapy. Because the nutraceuticals are not regulated by government agencies in the same manner as a drug would be, there is considerable variation in the composition and purity of the available products. Therefore, clinical results may vary considerably between the products.

The chondroprotective nutraceuticals usually contain **glucosamine salts** and/or **chondroitin sulfate**. Cartilage cells normally synthesize glucosamine from glucose and amino acids, however they can also use externally supplied, preformed glucosamine. Regardless of the source, the cartilage cells use glucosamine to synthesize glycosaminoglycans and hyaluronan. Glucosamine also regulates cartilage synthesis of proteoglycans and collagen.

Chondroitin sulfate (CS) is long chain molecule composed of galactosamine sulfate and glucuronic acid units. It is the predominant glycosaminoglycan found in joint cartilage and is a natural component of other tissues, including tendons, bone, vertebral discs, heart and cornea. Chondroitin sulfate stimulates glycosaminoglycan and proteoglycan synthesis in joint cartilage. It also inhibits destructive enzymes in joint fluid and cartilage.

**Dimethylglycine (DMG) (Vetri-cine® DMG; Vetri-Science DMG; Vitality Systems Equi-DMG; Vita-Flex Nutrition Co. Inc.)**

Dimethylglycine (DMG) is also a nutraceutical product, that is advocated for daily feeding to improving stamina and endurance by increasing oxygen utilization and improved lactic acid metabolism. Despite favourable anecdotal reports, DMG did not produce any beneficial effects on cardiorespiratory function or lactic acid production in exercising Thoroughbreds.

**Methylsulfonylmethane (MSM) (MSMO, Vitality Systems MSMO, Vita-Flex Nutrition Co. Inc.)**

Methylsulfonylmethane (MSM) is also a nutraceutical product, that is promoted as a bioavailable source of sulfur or a dietary derivative of dimethylsulfoxide (DMSO), a known anti-inflammatory agent. Sulfur is a necessary component of several amino acids, therefore MSM is promoted as helping to provide the "building blocks" for normal tissues, so it is thought to have some benefit in horses with degenerative joint disease. There are no published scientific studies documenting a beneficial effect from feeding MSM to horses.

**About the Author –**

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