

Down on the Farm



Treatment of Inflammation in Horses: Which Corticosteroids Are Effective?

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Inflammation is the process that the horse's body uses to defend and repair itself. Generally, inflammation is beneficial. This is particularly true in the defense of the body against bacteria and viruses that could potentially kill the horse. When bacteria invade the body, such as *Streptococcus* entering the lungs, they are rapidly killed by specialized cells called phagocytes. In the lung, phagocytes known as alveolar macrophages reside within the air passages. The macrophages are attracted to bacteria and, if there are few bacteria, the macrophages engulf and destroy them. If there are too many bacteria for the macrophages to handle, the macrophages send out chemical signals that attract other phagocytes known as neutrophils from the blood. By releasing a variety of chemicals that are capable of killing bacteria, the neutrophils rapidly overcome the infection. In the environment in which horses dwell, there are large numbers of bacteria that can enter lungs, the gastrointestinal system, cuts in the skin, and even the reproductive tract. Inflammation and the immune system constantly protect against these bacterial attacks. It is only when the horse's body is invaded by large numbers of bacteria or when the immune system is suppressed that inflammation cannot protect adequately against infection, and infectious disease results.

Inflammation is also beneficial for wound healing. It cleans the wound, brings in the right type of cells and blood constituents, and generally facilitates wound repair. Part of the tissue repair process is remodeling so that normal function is restored. Tissue remodeling also requires inflammation.

In some situations, however, inflammation is not beneficial to the horse. In these situations, inflammation is not provoked by infectious agents but is induced by non-lethal substances such as mold spores, insect bites or repeated strain. In these situations, the chemical substances within the neutrophils that normally kill bacteria are released

into the tissues where they do damage to the body itself. Some of the very common diseases of horses are results of this type of inflammation. In horses with heaves, inhalation of dusts and mold spores stimulates severe inflammation in the air passages. This inflammation causes the secretion of excessive amounts of mucus, stimulates coughing, and causes the muscles surrounding the air passages to go into spasm. The latter is known as bronchospasm. These processes are virtually identical to those that occur in human asthma, which is another inflammatory airway disease that is not due to infection. In addition to provoking cough, mucus secretion and bronchospasm, inflammation also leads to remodeling in the air passages. Rather than restoring normal airway anatomy, remodeling results in the formation of excessive numbers of mucus cells and more muscle around the air passages, both of which make breathing much more difficult.

Other examples of inflammation that are not beneficial include allergic skin diseases and certain types of non-infectious arthritis. In the latter case, repetitive strain on joints can initiate inflammation and remodeling of the joint so that it loses its flexibility.

In diseases in which inflammation is not occurring in response to infection, treatment involves reduction of the inflammatory response and the best drugs for this purpose are corticosteroids. However, these drugs should not be used to suppress inflammation that is a result of bacterial viral infection, because in these situations inflammation is essential to save the body.

Corticosteroids are very powerful drugs that control many aspects of inflammation. By interacting with genes, corticosteroids reduce the production of many of the chemicals that are essential for the migration of neutrophils to the site of inflammation and increase the production of chemicals that inhibit the inflammatory process. Corticosteroids also prevent the tissue remodeling that can occur as a result of inflammation.

The Pulmonary Laboratory at the Michigan State University College of Veterinary Medicine has been studying heaves for many years. The laboratory's investigations have recently focused on the efficacy of treatments for this disease. It is important to realize that the market for drugs to treat horses is trivial compared to the market for human drugs. Because the market is small and the cost of the studies to gain FDA (Federal Drug Administration) approval of a drug is so high, very few drugs are specifically approved for use in the horse, and veterinarians use many drugs "extra-label." That is, they use drugs approved for treatment of similar diseases in people or other animals. Such is the case with the use of corticosteroids for the treatment of heaves. Human asthma is very similar to heaves and corticosteroids are routinely used for the treatment of asthma. It is therefore very logical to use corticosteroids to reduce the inflammation that occurs in heaves. Indeed, this treatment for heaves has been used successfully for many years. Corticosteroids can be administered by injection, by mouth and, most recently, directly into the lungs by inhalation. From a practical point of view, it is easiest for the horse owner to give drugs by mouth mixed in with the feed.

Corticosteroids vary greatly in their potency and, unfortunately, the more powerful the corticosteroid then the more likely it is to have unwanted side effects. One of the reported side effects of corticosteroids in horses is laminitis, although the evidence in support of this relationship is scant. When treating a horse with heaves or other inflammatory disease, veterinarians must consider ease of administration, efficacy of the medication, and the possibility of side effects such as laminitis. For these reasons, veterinarians recommend administration of either prednisone, prednisolone or dexamethasone in the horse's feed. However, despite the frequency of use of these drugs, there had been no demonstration of their efficacy under controlled laboratory

conditions and no measurement of their absorption from the intestine, until our research group conducted a study that was funded by the SCEF (Southern California Equine Foundation).

Our interest in the efficacy of corticosteroids for the treatment of heaves began several years ago at the insistence of Dr. Cindy Jackson, an equine practitioner who was temporarily working in our laboratory. Research at many laboratories had demonstrated that keeping horses at pasture and preventing access to hay most effectively reversed the inflammation and airway obstruction associated with heaves. Dr. Jackson pointed out that this recommendation was not always possible to follow because many horse owners did not have access to pasture. She therefore suggested we do a "practical" research project that mimicked the situation in the real world where it might be possible to improve the environment in a single stall of a stable while at the same time administering a corticosteroid. The results of the study demonstrated that the airway

obstruction typical of heaves was greatly reduced when the affected horse was fed a complete pelleted diet and kept on shavings, even though the remaining horses in the stable were being fed hay and bedded on straw (Figure 1). The surprising finding from the study was that when horses received a corticosteroid in addition to being kept in a low-dust environment,

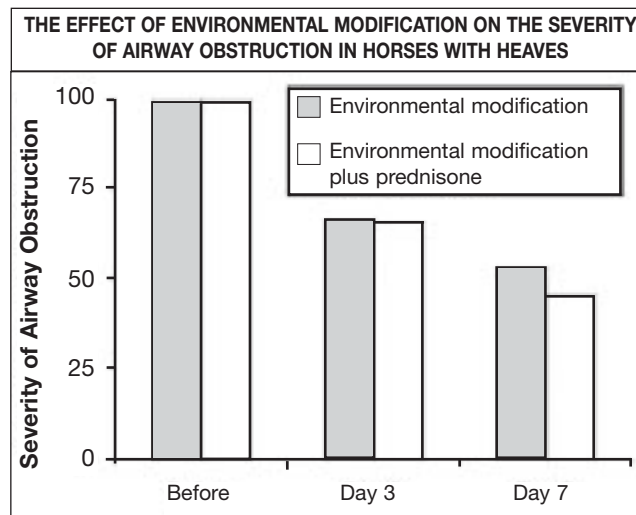
the corticosteroid provided no additional benefit. There were two ways to interpret this result:

- 1) the environmental effect is so powerful that corticosteroids are not necessary; or
- 2) the corticosteroid that we had selected, in this case prednisone, was not very effective. We chose to address the second possibility because prednisone is quite widely used for the treatment of many equine diseases. If it was not efficacious, it was important to find out as soon as possible.

To determine if pred-

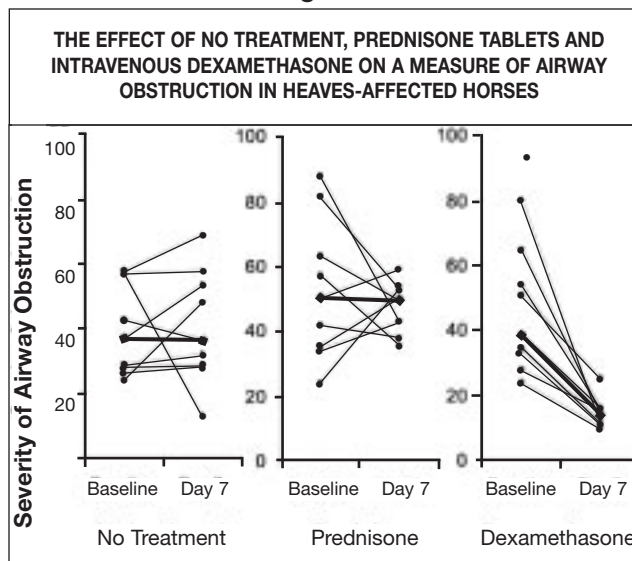
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Figure 1



When horses were switched from hay to pelleted feed, their airway obstruction improved within 3 to 7 days. Adding prednisone tablets did not add significant benefit.

Figure 2



Measurements were made before (baseline) and after seven days of treatment. Data from nine individual horses are shown with the mean value (dark line). Note the variable response to administration of prednisone and the consistent response to dexamethasone.

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nisonone had any efficacy for treatment of heaves, we compared the effect of prednisone tablets to both intravenously administered dexamethasone (a treatment previously demonstrated to be effective) and no treatment at all. During treatment, horses were kept on a hay diet so that environmental exposure remained constant. Figure 2 shows the severity of treatment at baseline (before treatment) and after seven days. Only one horse improved with no treatment and all nine horses improved greatly with dexamethasone treatment. Treatment with prednisone had variable effects on airway obstruction. Whereas some horses improved, others became worse. Overall, there was no mean improvement during prednisone treatment.

It is well-known that prednisone itself has no anti-inflammatory activity but must be absorbed from the gastrointestinal tract and metabolized by the liver into the active form prednisolone. Both prednisone and prednisolone can be administered by mouth. However, prednisone has been used extensively by equine veterinarians because it is available in conveniently-sized tablets for use in the horse. It is possible to purchase prednisolone but, in the U. S., no convenient form was available for the horse. Consequently, prednisolone was rarely used.

Knowing about the metabolism of prednisone to prednisolone, we decided to investigate if variable production of prednisolone after administration of prednisone might explain the variable efficacy of the latter drug. To complete the investigation of corticosteroid uptake from the gut, we also investigated the uptake of dexamethasone. This research project was funded by the SCEF and was a joint collaboration between the Pulmonary Laboratory at Michigan State University and the Kenneth L. Maddy Laboratory at the University of California, Davis. Dr. Dana Peroni did the drug administration and sample collection in Michigan and Dr. Scott Stanley and Dr. Cynthia Kollias-Baker at Davis did the assays. The results of the study demonstrated why the effect of administration of prednisone tablets had been so inconsistent for the treatment of heaves. When these tablets were given by mouth to six horses, the active ingredient prednisolone reached measurable levels in the blood in only one horse. By

contrast, when prednisolone itself was given to the horses, it appeared in high concentrations in the blood of every horse within 30 minutes to one hour of administration. Dexamethasone was also effectively absorbed from the intestine (Figure 3). By demonstrating that very little prednisolone was formed when prednisone tablets are administered to most

horses, we explained why prednisone was only inconsistently effective in treating heaves.

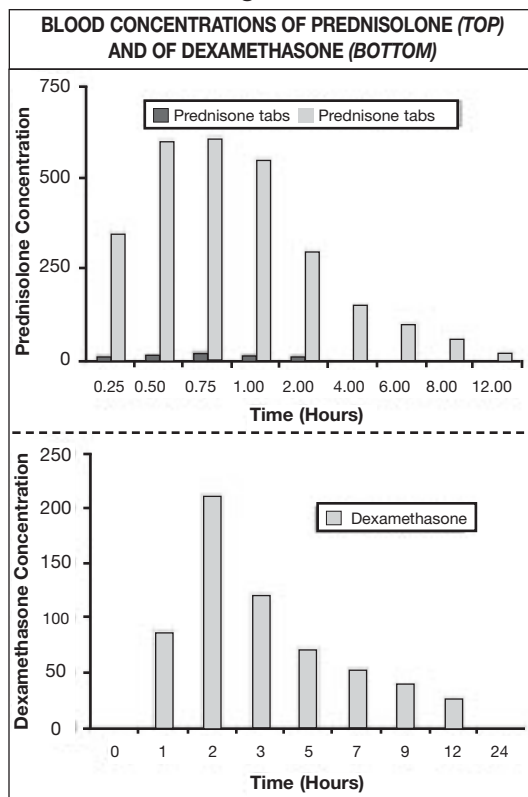
The results of the study have much broader implications in equine medicine than just the treatment of heaves. Orally administered corticosteroids are used for treatment of skin diseases, arthritis and some other problems. It is highly unlikely that prednisone is a very efficacious treatment for any of these problems. It would be much more beneficial to treat horses with prednisolone or dexamethasone. In the past, veterinarians have used prednisone because it was such a safe product. It was probably safe because it was relatively ineffective compared to other corticosteroids.

The practice of equine medicine keeps evolving and without studies such as we have performed, equine practitioners must rely on their experiences in the field to determine the efficacy of treatments. Every five years, I edit *Current Therapy in Equine Medicine*, a comprehensive textbook of treatments of horse diseases. This editorial task provides me with a snapshot of medical

progress related to the horse. I am currently editing the fifth edition and am struck by the increase in the information on the efficacy of medications. The studies that provide this sort of inflammation are not funded by the federal government but must be supported by private foundations or drug companies. Because pharmaceutical companies have a vested interest in proving efficacy of their compounds, grants from private foundations such as the SCEF are particularly valuable in searching out the truth about the treatment of horse diseases.

Dr. Ed Robinson is the Matilda Wilson Professor of Equine Medicine in the college of Veterinary Medicine at Michigan State University (MSU), where he directs the Pulmonary Laboratory. During his 30 years at MSU, Dr. Robinson has devoted his research career to understanding chronic airway diseases such as heaves in horses. Recently, he has been especially interested in "Evidence based medicine" (which treatments really are useful). In this light, he and his colleagues began investigating the usefulness of corticosteroids. They have continued his work with a grant from the Southern California Equine Foundation (SCEF). This article describes that work.

Figure 3



When horses received prednisone tablets, little prednisolone appeared in the blood. When they received prednisolone tablets, high concentrations appeared in the blood within 30 minutes. After administration of dexamethasone powder (Azium®), dexamethasone appeared in the blood within one hour.