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Rational Treatment of Inflammatory Airway Disease – Environment and Drugs

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Recurrent airway obstruction (RAO, or heaves) and inflammatory airway disease (IAD) are highly prevalent in stabled horses, and require treatment with corticosteroids and bronchodilators in addition to environmental modification. Topical application of bronchodilators and glucocorticoid drugs can help in avoiding the side effects and even toxicities associated with the systemic delivery of these drugs.

Treatment Strategy

The goals of treatment must be clear in order for there to be client, patient, and veterinarian satisfaction – this entails a team approach and an acceptance that this may be a life-long problem that may be modified but is unlikely to ‘go away’. Goals in treating RAO should include: 1) immediate relief of the bronchospasm that causes cough and dyspnea, 2) reduction of lower airway inflammation (neutrophils, mast cells, or both), 3) long-term prevention of episodes of heaves by control of lower airway inflammation and airway obstruction, and 4) return to limited or even full athletic potential. The goals for treatment of non-septic IAD are similar: 1) eliminate cough and bronchoconstriction that impair performance, 2) reduce mucus production and airway plugging, 3) reduce airway reactivity and 4) prevent recurrences. There is a place for aerosolized therapy in each one of these goals, although systemic corticosteroids are usually necessary for initial reduction of airway inflammation, and environmental control is paramount in long-term control of RAO. In order to achieve success, the veterinarian and client should plan for regular check-ups and be prepared for changes in treatment strategy that might be necessary. Owner education is critical in achieving compliance. Establishment of a reasonable definition of ‘return to athletic use’ is critical to client satisfaction. It is reasonable to look forward to returning a mildly affected, young racehorse to full racing potential. A reasonable goal for a horse with RAO might be a much more modest return to light pleasure riding. When available, lung function testing and response to bronchodilator can be very useful for identifying the horse that is less likely to respond to conventional therapy.

Monitoring Therapy

It is important to have a baseline assessment of the horse prior to initiating therapy. Ideally, this would include auscultation with and without a rebreathing bag, careful physical examination, observation during exercise, and baseline pulmonary function testing and measure of airway reactivity (IAD), or in the case of horses with RAO, the effect of bronchodilation, and bronchoalveolar lavage (BAL) cytology in either case. Although pulmonary function testing is currently available only at a few specialized veterinary pulmonology clinics, it is likely that user-friendly systems for field-testing will soon be available, making objective baseline assessments
available to practitioners. The goal of a thorough baseline assessment is to facilitate a treatment regimen tailored to the individual horse, and to monitor response to therapy. At our pulmonary clinic, we offer free lung function testing one month after initiation of therapy to assess response to therapy and fine tune therapy for the upcoming months. We also encourage telephone and email communication with owners and referring veterinarians in order to facilitate this process.

Environment

The first and most important treatment – environmental remediation – is also the most long lasting and free of side effects, but many owners are reluctant to fully pursue this path. The following evidence may serve as greater impetus to do so. Multiple studies have shown that environmental remediation, usually meaning pasture with pelleted complete feed and complete cessation of hay feeding, results in almost complete remission from RAO. If pasture is not available, then cardboard bedding accompanied by complete pelleted feed is a suitable alternative. A randomized controlled study demonstrated that a combination of complete pelleted feed and outdoor living resulted in remission in heavy horses, using PFTs and BAL to confirm. Only in severe cases was the addition of inhaled fluticasone propionate necessary. Subsequently, this group has shown that RAO horses kept in low dust environments with no medical management for up to 5-6 years are indistinguishable from a control group without probing the lower airways via measurements of FEV. We commonly recommend that horses be removed from the barn when stall-cleaning or any other barn cleaning is done, as this is a time when airborne particulates are very high. Likewise, we recommend that when possible, horses eat outside, as eating is also associated with a high respirable particulate load. There are, however, some horses – not just those in the South, with Summer Pasture Associated Recurrent Airway Obstruction (SPARAO) – that seem to have the worst exacerbations of airway obstruction during warm, humid summer weather. This may be because airborne endotoxin loads are highest outside during the summer. It may also be due to mold blooms on unthatched pastures. We encourage owners to keep a diary of disease exacerbations and possible exposures in order to gain a more balanced view of the best environment for each horse.

Short-Term Drugs: Beta 2-Agonists

Beta2 agonists work by increasing the production of adenylate cyclase; they thereby increase intracellular cAMP levels with subsequent relaxation of airway smooth muscle.

Short-acting β2 agonists such as albuterol and fenoterol, are of vital importance in treatment of acute exacerbations of RAO. The horse that is laboring to breath and has paroxysmal coughing will experience rapid relief with the use of β2 agonists. However, these are correctly termed ‘rescue drugs’, and should not be used on a regular basis. It is important to remember that the inflammatory condition will persist despite apparent improvement due to transient bronchodilation, and the disease will worsen. Regular use of β2 agonists in the absence of anti-inflammatory medication may mask symptoms that would otherwise indicate progressive worsening of the disease in particular, further airway obstruction with mucus.

Short-acting β2 agonists are not performance enhancing in humans, and increasing evidence supports this finding in horses. Nonetheless, albuterol and similar drugs remain proscribed by all
equine sporting events, and due care should be taken to stop drug administration before competition. Short-acting $\beta_2$ agonists can be useful in horses with IAD and underlying airway obstruction to improve the return to training. Administration of albuterol may also increase the peripheral lung deposition of other concurrently used drugs. Short-acting bronchodilators are also useful during lung function testing to assess the reversibility of airway obstruction in horses with RAO. No more than 450mg of albuterol by inhalation is necessary to bronchodilate most horses, irrespective of the delivery device chosen.

Although aerosolized $\beta_2$ agonists have a relatively low incidence of side effects, excessive use or sensitive individuals may experience systemic effects such as trembling, anxiety and cardiac arrhythmias. The author has noted all these in individuals treated with 900 micrograms of albuterol, whereas other individuals show no signs of intolerance. Repeated use of the drug tends to decrease side effects as the body down regulates receptors. Very occasionally, horses may exhibit signs of bronchoconstriction to $\beta_2$ agonists. This paradoxical response is likely due to the effects of the drug vehicle on airways and is transient.

**Short-Term Benefits: Anticholinergics**

Both cough and bronchoconstriction are vagally mediated, thus parasympatholytic drugs (such as ipratropium bromide) are effective in mitigating these. As with any parasympatholytic drug, there is a potential for tachycardia, thickened mucous, decreased ciliary beat frequency, and decreased mucociliary clearance, however, studies in horses have showed no such side effects with doses up to 1200 micrograms. The index of safety is considerably greater than systemically administered atropine. Ipratropium has a slower onset of action than albuterol, and its actions seem to be confined primarily to the central (larger) airways rather than bronchioles. Studies in horses suggest that pulmonary function begins to improve 15 minutes after administration, and although duration of action has only been verified through one hour, clinical evidence suggests that horses experience relief for up to 4 to 6 hours. Although ipratropium may act as a useful adjunct to $\beta_2$ agonists for a rescue treatment during exacerbations of RAO, it is not the primary treatment of choice due to its slower onset of action. In horses with adverse responses to $\beta_2$ agonists, ipratropium bromide may be preferred.

**Long-Term Control: Corticosteroids**

Corticosteroids remain the cornerstone of successful treatment for both IAD and RAO. The use of inhaled corticosteroids has truly revolutionized the treatment of RAO and IAD. While initial systemic tapered corticosteroid therapy is often necessary with all but very mild IAD, regular inhaled therapy is essential for long-term success in most cases. Inflammation underlies remodeling of the airways with accompanying airway hyperreactivity, or increased ‘twitchiness’ of the airways, and consequent coughing and expiratory dyspnea. Bronchodilator drugs will help to relieve acute, debilitating bronchospasm, but only consistent anti-inflammatory therapy, in conjunction with avoidance of environmental triggers, will break the vicious cycle of inflammation, airway hyperreactivity, and bronchoconstriction. The most important factor in limiting regular use of inhaled corticosteroids is cost: drugs such as fluticasone (Flovent®) and beclomethasone (QVAR®) are very expensive.
The anti-inflammatory effect of corticosteroids in both RAO and IAD is impressive. Corticosteroids activate glucocorticoid receptors, thus putting into motion a profound inhibition of the arachidonic acid cascade and limiting production of leukotrienes and other inflammatory molecules. Response to steroids can vary considerably from horse to horse. RAO horses treated with beclomethasone dipropionate have shown both objective and subjective evidence of decreased airway obstruction, as well as a decrease in pulmonary neutrophilia within 24 hours of initiation of therapy. Doses range from 500 micrograms to 1200 micrograms when using the HFA formulation. Although there is evidence of adrenal (HPA)- hypopituitary (i.e., reduced serum cortisol levels) suppression with all doses \( \geq 500 \text{mg} \), this does not pose a risk of chronic HPA suppression or rebound Addisonian crisis. Fluticasone propionate decreases pulmonary neutrophilia, improves pulmonary function, and reduces airway hyperreactivity in RAO-affected horses. Fluticasone propionate is the most potent of the inhaled corticosteroids, has the longest pulmonary residence time, and causes the least adrenal suppression. Newer formulations of beclomethasone dipropionate that incorporate HPA as the propellant have more uniform particle size, and are more uniformly mixed, requiring little to no agitation or waiting before actuation of the inhaler.

The general strategy pursued at the pulmonary clinic at Tufts University School of Veterinary Medicine is to treat in a stepwise manner, starting with a high dose given frequently, with a gradual reduction in therapy until the lowest effective dose can be found. If owners are vigilant in environmental control and are compliant with treatment recommendations, many horses can eventually be treated successfully on an every other day basis to prevent recurrences. Some owners have been successful in documenting seasonal exacerbations: in this case we recommend beginning treatment with inhaled corticosteroids and, occasionally, mast-cell inhibitors, at least two weeks before the anticipated allergen season. It is important to remember, though, that unless all stimuli for pulmonary inflammation is removed, the effect of inhaled corticosteroids is transient, and symptoms will return when the horse is exposed to organic dust and other allergens. Corticosteroids should not be used for quick-relief, or rescue therapy, as the onset of action is at least 24 hours, and several months of regular use may be necessary for optimum results. With severe inflammation, systemic corticosteroids are usually necessary to achieve break-through before initiating inhaled therapy. Most horses with RAO and RAD will require loading doses for 2-4 weeks of systemic steroids before reliance on aerosol medications although trials are lacking that demonstrate the effective preventative dose.

**Mast Cell Inhibitors**

Mast cells are important mediators of inflammation in horses with IAD or RAO, with studies linking mast cells with airway reactivity, environment, and levels of inflammatory mediators in lavage (ie BAL) fluid. These drugs stabilize the mast cell membrane, thus blocking degranulation and inhibiting the allergic response at an early stage. These drugs have a tendency to cause cough and aversion (perhaps due to a bad taste) in horses. There is anecdotal evidence that pre-treatment with albuterol may attenuate some of the cough response.

Their greatest therapeutic effect is seen when given a long-term therapy and prior to exposure to allergen such as before allergy season or before transporting a horse to a new environment. There is, understandably, less customer satisfaction and, consequently poorer compliance, with drugs...
that do not have a visibly dramatic effect, such as the $\beta_2$ agonists and even the potent corticosteroids.

**Long-Acting Beta 2-Agonists**

We treat selected cases of RAO and moderate IAD with long-acting $\beta_2$ agonist (LABA) therapy in addition to inhaled corticosteroids, with the initial impression of enhanced performance and quality of life. It cannot be emphasized enough, however, that regular use of long acting $\beta_2$ agonists *must be accompanied with regular use of inhaled corticosteroids*. The most commonly used LABAs are salmeterol and formoterol, whose basic mechanism of action is the familiar cAMP pathway. Their duration of action in horses is 6-8 hours.

*When the Patient Does not Respond to Therapy*

If there is poor response to therapy, it is important to do some detective work to determine why treatment has been unsuccessful. It is essential to check the client’s technique for using the drug delivery device. Failure to modify the environment may, in some horses, negate any attempts at drug therapy. Some horses with chronic, severe pathology may be resistant to corticosteroids or may have irreversible changes in the lungs that prevent response to bronchodilators. Finally, lack of response to therapy may be due to underlying infectious disease and may indicate the need for further diagnostics and perhaps an entirely different approach or concomitant antibiotic use.