Proceedings of the 50th British Equine Veterinary Association Congress BEVA

Sep. 7 – 10, 2011
Liverpool, United Kingdom

Next Congress:

14.30–15.00

Systemic anti-inflammatory therapy for LRT disease

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The airway obstruction and pulmonary dysfunction, and consequent morbidity and mortality, that are associated with lower respiratory tract (LRT) diseases, are attributable largely to inflammation. Consequently, anti-inflammatory agents have an important role in the management of most LRT disorders. Ideally these agents should be used in conjunction with treatment targeted at the underlying aetiology, such as provision of an organic dust-free environment in the case of recurrent airway obstruction (RAO). Furthermore, it is important to recognise that, because anti-inflammatory agents afford no *immediate* improvement in airway function, they should be used in conjunction with bronchodilators in horses with significant LRT obstruction. Systemic anti-inflammatory drugs may be more beneficial than inhaled drugs because aerosolised drugs are poorly distributed in the lungs of horses with diffuse severe airway obstruction.

Glucocorticoids

Glucocorticoids, administered systemically or by inhalation, effectively attenuate pulmonary inflammation in many LRT diseases including RAO, summer pasture associated obstructive pulmonary disease (SPAOPD) and inflammatory interstitial lung disease. Glucocorticoid administration is also indicated in IAD, especially for refractory cases and cases which have an eosinophilic or mast cell dominated cytological pattern. Glucocorticoids are the only agents which reduce nonspecific bronchial hyper-responsiveness, which is responsible for much of the pulmonary dysfunction associated with LRT inflammation. Prednisolone (1 mg/kg bwt *per os* q. 24 h) and dexamethasone (0.04–0.1 mg/kg bwt i.v. q. 24 h) are most commonly used. Both corticosteroids improve pulmonary function in RAO horses, in spite of continuous organic dust exposure. However, oral dexamethasone at 0.05 mg/kg bwt is more effective than prednisolone at 2 mg/kg bwt in the treatment of RAO. These agents afford no immediate improvement in airway function, but clinical signs, lung function and inflammation improve by 6–72 h. Dexamethasone improves lung function maximally by Day 7, with i.v. administration producing measurable therapeutic benefit within 2 h and *per os* administration within 6 h. Following cessation of one week of treatment, some therapeutic benefit can be detected 7 days later. Unlike prednisolone, dexamethasone markedly suppresses endogenous cortisol production, an effect which persists for several days after drug withdrawal. A long-acting preparation of dexamethasone (dexamethasone 21-isonicotinate 0.06 mg/kg bwt i.m. q. 14 days) reduces airway obstruction by Day 3, with a maximal effect achieved by Day 7. Oral prednisone is ineffective in most horses because of poor bioavailability. Triamcinolone acetonide (0.09 mg/kg bwt i.m. single dose), one of the most potent systemic corticosteroids, relieves airway obstruction for up to 4 weeks; however, adrenal suppression is evident for 4 weeks following administration. Repeated administration of triamcinolone has been reported to induce iatrogenic Cushing's syndrome, adrenal insufficiency and laminitis and therefore should not be used to treat pulmonary inflammation.

Sodium cromoglycate

Sodium cromoglycate has been used as a prophylactic medication to control RAO, however recent studies were unable to demonstrate efficacy.

Leukotriene receptor antagonists

Leukotriene receptor antagonists are beneficial in many human asthmatics. However montelukast (0.11 mg/kg bwt *per os* q. 24 h), a cysteinyl leukotriene receptor antagonist, is ineffective for treatment of RAO, possibly because of poor bioavailability following oral administration. While the leukotriene D4 receptor antagonist L-708,738 (2.5 mg/kg bwt *per os* q. 12 h) has demonstrable bioavailability after oral dosing and achieves plasma drug concentrations exceeding *in vitro* efficacy values, airway function does not improve after 14 days of administration, suggesting that cysteinyl leukotrienes are not pivotal mediators of airway inflammation in RAO.

Antihistamines

Antihistamines are commonly used and often effective treatments for human hypersensitivity disorders, but are relatively ineffective in equine hypersensitivity disorders.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have little efficacy in equine LRT inflammation.

Immunotherapy

Immunotherapy has not been evaluated in properly designed and controlled studies, although there are anecdotal reports that it may be beneficial in some horses with RAO.

Dietary antioxidants and omega-6 and omega-3 fatty acid supplementation

Dietary antioxidants and omega-6 and omega-3 fatty acid supplementation have no proven efficacy in equine LRT diseases. Antioxidant supplementation should be theoretically beneficial by attenuating oxidant mediated pulmonary damage. While dietary antioxidant supplements increase the concentration of antioxidants in the pulmonary epithelial lining fluid, consequent improvements in clinical indices of horses with LRT diseases have not been reported. N-acetylcysteine is frequently administered as an expectorant, mucolytic and antioxidant, but its use in horses has not been critically evaluated and efficacy data are required before this drug can be recommended. In human medicine, acetylcysteine does not aid clearance of secretions and may even be an irritant.

β_2-agonists

β_2-agonists, such as clenbuterol, induce bronchodilation, increase mucociliary clearance and have beneficial anti-inflammatory actions. Clenbuterol treatment of RAO horses prior to hay dust exposure not only improved lung function, but also reduced bronchoalveolar lavage fluid total cell and neutrophil counts and decreased alveolar macrophage TNF-alpha, IL-1 and IL-8 expression. However, regular administration of β_2-agonists to human asthmatics results in deterioration in pulmonary function, increased airway responsiveness and more frequent exacerbations of bronchoconstriction. This is in part attributable to down-regulation of β_2-receptors by pulmonary inflammation, which reduces drug efficacy. Concomitant administration of glucocorticoids reduces this receptor down-

regulation and induces formation of new β_2-receptors on pulmonary cells. It is therefore recommended that β_2-agonists should only be used as short-term rescue drugs and that airway obstruction should be addressed primarily by environmental control and by anti-inflammatory drugs. Furthermore, prolonged use (≥12 days) of β_2-agonists results in tachyphylaxis which further limits their clinical benefit. Rapid i.v. administration of β_2-agonist bronchodilators to acutely dyspnoeic horses may temporarily (lasting up to 4 h) reduce PaO_2 concentration, possibly due to drug induced pulmonary vascular dilation which exacerbates *V/Q* mismatching. While this effect is probably of little clinical significance in most dyspnoeic horses, there are anecdotal reports of significant, life threatening exacerbations in some horses which have profound hypoxaemia. This adverse effect may be attenuated by pretreatment of horses with intranasal oxygen prior to administration of β_2-agonists, or avoided using other classes of drugs (such as atropine).

Further reading

Rush, B.R. and Davis, E.G. (2006) Pharmacology and therapeutics of pulmonary medications. In: *Equine Respiratory Medicine and Surgery*, Eds: B.C. McGorum, P.M. Dixon, N.E. Robinson and J. Schumacher, Elsevier, Edinburgh.

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