In an Adult Horse With Severe Asthma (Previously Recurrent Airway Obstruction) Does Using Inhaled Corticosteroids Result in an Equal Improvement in Clinical Signs When Compared to Systemic Corticosteroids?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

In an adult horse with severe asthma (previously recurrent airway obstruction (RAO)) does using inhaled corticosteroids result in an equal improvement in clinical signs when compared to systemic corticosteroids?

Clinical bottom line

The level of confidence in the outcomes from the body of evidence in the 4 papers identified is high.
This suggests inhaled corticosteroids (fluticasone and beclomethasone) when used at an appropriate dose can have equivalent effects on severe equine asthma as systemic intravenous dexamethasone. Inhaled corticosteroids can take longer to have the desired effects.

Clinical Scenario

A 12-year-old cob mare presents to you with increased respiratory effort and rate at rest. Radiographs and ultrasound of the lungs are unremarkable. A bronchoalveolar lavage indicates inflammation and neutrophilia (>20% neutrophils) with no evidence of bacterial infection. You diagnose equine severe asthma (previously called recurrent airway obstruction) and need to decide the best treatment option for the mare. The owner is concerned with the potentially long term use of systemic steroids and wants to know if other routes of administration for steroid treatment are effective.

The Evidence

Following refinement of the initial search and exclusion of unsuitable publications, four studies were found that were directly applicable to the PICO question (Rush et al. 1998; Couëtil et al. 2005; Couëtil et al. 2006; Robinson et al. 2009). All four were clinical trials, with three being crossover in design (Rush et al. 1998; Couëtil et al. 2006; Robinson et al. 2009). Three were blinded (Rush et al. 1998; Couëtil et al. 2005; Couëtil et al. 2006). None of the studies were completely comparable because each had slightly different interventions and outcomes but overall the evidence was of high quality.

Summary of the evidence

Rush (1998) – published as 3 parts but one study	
Population:	Adult horses with a diagnosis of severe equine asthma Recurrent Airway Obstruction (RAO) which could be induced with the moldy hay challenge.
Sample size:	6
Intervention details:	Severe equine asthma was induced via the moldy hay challenge over 7 days. Then in a cross over design the following were administered for 7 days: - Inhaled beclomethasone (1,320µg twice a day (BID)) via 3M metered dose delivery device + 20mls saline IV SID - IV Dexamethasone (0.1mg/kg once a day (SID)) + aerosolized

	propellant (10 actuations BID) - Aerosolized propellant (10 actuations BID) + 20mls saline IV SID Horses were maintained in the moldy environment for a further 7 days. There was a two-month washout period between treatments.
Study design:	Prospective crossover, blinded, controlled clinical trial
Outcome studied:	Clinical scoring (BID days 0-21) plus pulmonary function testing (max trans pulmonary pressure change, pulmonary resistance and dynamic compliance) and bronchoalveolar lavage were performed at days 0, 7, 10, 14 and 21.
Main findings: (relevant to PICO question):	• Clinical score and pulmonary function improved after 3 days of beclomethasone compared to the control. The improvement was greater with IV dexamethasone compared to beclomethasone. • The beneficial effects actions of beclomethasone did not extend beyond the treatment period for clinical score outcome but did for pulmonary function. • Bronchoalveolar lavage cytology identified neutrophilia induced by the moldy hay challenge which was significantly improved by both corticosteroids. The neutrophilia rebounded after treatment discontinuation for both treatment options.
Limitations:	Small sample size
Couëtil (2005)	
Population:	Adult horses with a history consistent with severe equine asthma (RAO)
Sample size:	28
Intervention details:	Horses assigned to either mild, moderate or severe clinical groups based on initial clinical examination and pulmonary function testing. Horses within each group were randomly assigned to one of the following treatments: - Inhaled fluticasone via metered dose inhaler using Equine Aeromask™ - Inhaled control substance - Oral prednisone All 3 treatments were given in a tapering regime over 4 weeks. All horses kept outdoors at pasture and fed a pelleted feed for duration.
Study design:	Prospective, randomised, double blind, controlled clinical trial
Outcome studied:	Clinical scoring, pulmonary function testing (extensive) and bronchoalveolar lavage were performed at week 0, 2 and 4.

Main findings: (relevant to PICO question):	• In those animals with the most marked disease, treatment with fluticasone (1980µg BID) for 2 weeks had a significant improvement in pulmonary function compared to prednisone or control. • Irrespective of treatment group all animals had improved clinical scores over the 4 weeks indicating environment is critical. • Cytology of bronchoalveolar lavage was not statistically different between the groups.
Limitations:	• Various degrees of severe equine asthma with various confounding factors prior to enrollment. • 54% were discharged for treatment by owner at home. • Prednisone is a pro drug considered to have low bioavailability, inefficiently converted in the horse and not available in the UK. • Only 1 of the treatment options given to each horse.
Couëtil (2006)	
Population:	Adult horses with a diagnosis of severe equine asthma (RAO). Diagnosis by asthma induction following moldy hay challenge, with abnormal pulmonary function testing, >25% neutrophilia in BAL and normal haematology and biochemistry.
Sample size:	7
Intervention details:	Severe asthma was induced via the moldy hay challenge. Then in a crossover design the following were administered: - Inhaled beclomethasone dipropionate, 500µg BID for 10 days using 3M hand held delivery device - A single IM injection of dexamethasone 21-isonicotinate 0.06mg/kg - A single IM injection of sterile saline A 4 week wash out period between interventions was employed with repetition of the moldy hay challenge before each intervention.
Study design:	Prospective crossover, blinded, controlled clinical trial
Outcome studied:	Clinical scoring (days 0, 1, 4,7,10), pulmonary function testing (max trans pulmonary pressure change, pulmonary resistance and dynamic compliance), bronchoalveolar lavage and bronchial brushing (day 0 and 10)
Main findings: (relevant to PICO question):	• 10 days of low dose inhaled beclomethasone significantly improved pulmonary function but failed to alter airway cytology or clinical score • A single injection of long acting dexamethasone failed to improve any of the outcome variables examined
Limitations:	• Under powered. • Low dosage of drugs used. • Short study period. • Randomisation not described.

	• No inhaled control substance.
Robinson (2009)	
Population:	Adult horses with previous diagnosis of severe equine asthma (RAO) which demonstrated atropine-reversible airway obstruction when housed and fed hay.
Sample size:	8 in first protocol and 6 in second
Intervention details:	Two protocols 1) Severe asthma was induced via stabling on straw and hay. Then in a crossover design the following were administered for 3 days: - Fluticasone 3mg inhaled BID using Equine Haler™ - Fluticasone 6mg inhaled BID using Equine Haler™ - Dexamethasone 0.1mg/kg SID IV A 21-day washout period at pasture with a pelleted diet between the 3 treatments was undertaken. 2) Animals which had been at pasture for 21 days were confirmed to be in remission, and then in a cross over design the following were administered for 7 days: - Fluticasone 6mg inhaled BID using Equine Haler™ - Dexamethasone 0.1mg/kg SID IV - No treatment For the first 3 days horses remained at pasture then moved into stables on straw and fed hay. A 21 day washout period at pasture with a pelleted diet between the treatment protocols was undertaken.
Study design:	Prospective, non-blinded, crossover, controlled clinical trial
Outcome studied:	1) Clinical scoring (respiratory and lameness) and pulmonary function testing (maximal change in pleural pressure) (0, 24, 48, 72hrs) and bronchoalveolar lavage (0 and 72hrs). 2) Clinical scoring (respiratory and lameness) and pulmonary function testing (days 0, 4-8), bronchoalveolar lavage (days 0 and 8).
Main findings: (relevant to PICO question):	• Inhaled fluticasone at a dose of 6mg BID, but not 3mg BID, significantly improved respiratory clinical score and pulmonary function in horses with active asthma but only after 72 hours of treatment. • Intravenous dexamethasone was equally effective but had a faster onset of 24 hours after treatment initiation. • Both corticosteroids were effective when compared to no treatment at preventing acute exacerbation of asthma. • No significant difference in bronchoalveolar lavage cytology was seen with any of the treatments or doses in either protocol. • No signs of acute laminitis were observed in either protocol

	using the clinical lameness scoring.
Limitations:	• Short study period (3 days of treatment only for initial study and 8 days for 2nd protocol). • Ideally the control group should have received placebo (inhaled +/- IM injection). • Low sample size and not blinded. • Limited pulmonary function tests.

Appraisal, application and reflection

Three out of the four studies (Rush et al. 1998; Couëtil et al. 2006; Robinson et al. 2009) used a very similar design which involved inducing clinical disease by exposure to hay and or straw, using highly controlled environments and comparing inhaled and systemic corticosteroids to a control. The studies used clinical scoring systems for assessment of clinical signs, and used other similar outcome measures such as BAL cytology and pulmonary function testing, which allowed comparison between studies. All three of the above studies used pleural pressure changes to initiate the start of the treatment period, with the cut off value being equivalent in Rush et al. (1998) and Couëtil et al. (2006), and similar in Robinson et al. (2009). The populations were different and geographical location also varied. As is often the case, the clinical trials used small numbers of animals and relatively short study periods Treatment protocols varied from three days to four weeks with the largest and longest study (Couëtil et al. 2005) being the least controlled. Couëtil et al. (2005) differed in methodology to the other papers but, importantly, it was not crossover in design and still employed clinical scores, pulmonary function and cytology to compare the groups.

Two different inhaled corticosteroids were investigated (beclomethasone and fluticasone) in all four studies, but at different doses. Two studies (Rush et al. 1998; Robinson et al. 2009) used systemic dexamethasone at the same dose for varying lengths of time. The two studies that compared systemic dexamethasone to the inhaled steroids found them to be broadly equivalent at specific doses except that the onset of beneficial actions was slower with the inhaled steroids.

The other two studies found that the systemic corticosteroid used, either oral prednisone (Couëtil et al. 2005) or a long-acting intramuscular preparation of dexamethasone (Couëtil et al. 2006), was not effective. The low bioavailability of prednisone in horses makes its use in the Couëtil et al. 2005 paper highly questionable. Couëtil et al. (2005) also modified the environment for all animals. This had a significant effect on outcome, which may have confounded the results. Two studies used the same inhaler device (Hand held metered device 3M™) for administering beclomethasone (Rush et al. 1998; Couëtil et al. 2006) whereas the other two used different devices, thus adding a further potential variable when comparing the studies.

Only one study (Rush et al. 1998) observed significant differences in airway cytology, specifically reduction in BAL neutrophilia, as a result of corticosteroid treatment. BAL is widely used for diagnosis and monitoring of equine severe asthma but the evidence from the other three of these studies suggests it may not be a useful outcome for monitoring response to treatment.

The available evidence is of sufficient quality that clinicians should be able to apply the findings to clinical scenarios. The most effective inhaled corticosteroid appears to be fluticasone at 6mg BID which seems to be able to prevent exacerbation of asthma in horses moving from pasture to a stabled environment. The use of IV dexamethasone may be preferable in the acute case as the onset of clinically-apparent action was reported in these studies to be faster. The literature is lacking comparison of inhaled corticosteroids and prednisolone. Prednisolone is a widely used oral corticosteroid in the UK with a product licensed for equine asthma specifically. Since these studies were published, ultrasonic nebulisers (which provide an alternative to metered dose inhalers as a means of delivering inhalation therapy) have come to the market in the UK and these also warrant comparison in clinical settings.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts 1973- week 29 2017 Pubmed 1900- week 29 2017
Search terms:	Equine or horse and recurrent airway obstruction or RAO or equine asthma and corticosteroids or corticoids
Dates searches performed:	19/07/2017

Exclusion / Inclusion Criteria	
Exclusion:	Articles not relevant to the PICO question, in vitro studies, book chapters or conference proceedings.
Inclusion:	Relevant to PICO question, more than 1 animal, in vivo

Search Outcome

Database	Number of results	Excluded – irrelevant to PICO question	Excluded – duplicates	Excluded – Conference proceedings or review articles	Excluded – in vitro studies	Total relevant papers
CAB Abstracts	23	20	0	2	0	1
PubMed	37	30	1	0	3	3
Total relevant papers when duplicates removed						**4**

CONFLICT OF INTEREST

The author declares no conflict of interest.

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