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Inhalation therapy for equine lower respiratory disease

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Introduction

The delivery of drugs to horses via the inhalation route is an increasingly adopted therapeutic approach in equine practice, predominantly aimed at the treatment of equine lower airway disease, including, but not restricted to, both severe and mild to moderate equine asthma (previously termed Recurrent Airway Obstruction [RAO] and Inflammatory Airway Disease [IAD], respectively) and Exercise Induced Pulmonary Haemorrhage. Like many therapeutic approaches, there are both advantages and disadvantages associated with inhalation therapy which must be considered when selecting the most appropriate treatment on a case-by-case basis. Additionally, there are a number of unanswered questions with respect to inhalation therapy in the horse, most notably in relation to the efficiency and variability of drug delivery to the lower airways which, considering the specific equine airway diseases in which inhalation therapy is commonly applied, constitutes the principal target site (i.e. small and terminal airways) of drug deposition. Even in the absence of lower airway disease, achieving such drug deposition within a system designed to avoid particle penetration of the lungs can be challenging. This review provides an overview of the principals of inhalation therapy, the advantages and disadvantages of this approach, the techniques commonly used to administer inhaled medication and the drugs commonly administered via the inhaled route.

General principles of inhalation therapy

Inhalation therapy describes the delivery of drug directly to the airways, a process which relies on the generation of an aerosol containing microdroplets of medication, either generated from a liquid reservoir or consisting of dry powder. Atomisation of liquids is generally achieved by jet, ultrasonic or mesh nebulisation or by the use of a pre-calibrated metered dose inhaler device. Each method of liquid atomisation differs with respect to the properties of the aerosol generated (i.e. particle size distribution).

For the purpose of this article, the target site will be regarded as the lower airways, bearing in mind that, in certain rarer circumstances, the aim of inhalation therapy may be to maximise drug deposition more proximally in the respiratory tract (e.g. nasal cavity or trachea). The particle size distribution of the generated aerosol constitutes a major determinant of the likelihood of the aerosolised drug reaching the lower airways; however other factors also play a role in determining the efficiency of this delivery (summarised in Table 1). It should be emphasised that the aerosol particle size distribution considered optimal for drug delivery to the equine smaller airways is largely based on human patient derived data. The American Conference of Governmental Industrial Hygienists (ACGIH) generally assumes the aerodynamic diameter of aerosolised particles within the *respirable fraction* (defined as the aerodynamic diameter at which 50% penetration of that fraction occurs) to be 4 micrometres. Although the likelihood of significant differences between the size-dependent penetration of particles into the equine and human lung has been proposed (Ivester et al, 2014), in the absence of experimental data to define equine-specific particle fractions, it is generally assumed that particles less than 4-5 micrometres are likely to reach the lower airways in the horse (Hoffman, 1997; Lavoie, 2001). Larger particles will deposit in the larger airways via a process of inertial

impaction and particles less than 0.5 micrometres will likely be expired within the exhaled breath (Duvivier et al 1997).

A number of factors influence the particle size distribution of the generated aerosol. These include factors associated with the method of aerosol generation (e.g. air flow rates during jet nebulisation) and factors inherent to the aerosolised solution (e.g. density, viscosity, surface tension and hygroscopic growth potential; Table 1) (Duvivier et al 1997). Other particle dependent determinants of lower airway deposition include electrostatic charge and particle shape. Therefore, the assumption that all aerosolised drugs are likely to share the same distribution properties is false and data are very much lacking on the aerosol distribution properties of many medications which are increasingly administered by the inhalation route in equine practice. Variations in properties such as viscosity will *directly* influence the particle size distribution and factors such as tonicity (e.g. hypotonicity) may *indirectly* influence lower airway deposition via the induction of a protective bronchoconstrictive response (Table 1). Most medications intended for inhaled administration are isotonic, a potentially important factor when considering the administration of other drug formulations (e.g. drugs formulated for intravenous use) via the inhalation route. Furthermore, such formulations may also contain other components (e.g. preservatives) which result in bronchoconstriction, thus further compromising their deposition within the smaller airways. For example, human studies evaluating the use of inhaled tobramycin (with and without phenol preservatives), aztreonam and colistin confirmed the induction of significant and acute, yet transient, bronchoconstriction following inhalation (Hodson *et al*, 2002; Nikolaizik *et al*, 2002; Retsch-Bogart *et al* 2008). Such effects were attributed to osmolality and preservatives within some of the solutions and recommendations were made to routinely administer bronchodilators before dosing.

In addition to particle dependent factors, a number of patient dependent factors influence lower airway deposition (Table 1). It has been proposed that the horse constitutes a highly appropriate subject for inhalation therapy due to its high inspiratory flow rates and the prolonged drug retention times which result from the relatively low breathing frequency. However, for dry powder inhalation at least, excessively high flow rates have been shown to promote impaction in the upper airways with lower flow rates enhancing sedimentation and therefore more distal deposition of the aerosol (Timsina et al 1994). Furthermore, compliance with the technique of administration will vary greatly between individuals, with some horses becoming agitated and increasing their breathing frequency and others adopting prolonged periods of breath-holding. Indeed, it may be deemed dangerous to persist with inhalation therapy in some horses which become distressed during the administration procedure. This disparity in breathing pattern will inevitably contribute significantly to the variation in drug deposition between both patients and treatment episodes. Unfortunately, the standard technique employed in human inhalation therapy, consisting of a slow inhalation followed by a period of breath holding, cannot be applied to horses due to the voluntary nature of this manoeuvre.

Adequate ventilation of the diseased lung is a necessary requirement for successful inhalation therapy and any detected or anticipated compromise in ventilation should be considered prior to embarking on this mode of drug delivery (Table 1). For example, a case of severe equine asthma with significant lower airway obstruction (e.g. bronchospasm, mucus plugging) is unlikely to benefit from the delivery of drugs via the inhalation route, at least until the obstruction is partially relieved via other therapeutic approaches. In such cases, the degree of lower airway obstruction will be reflected in the altered breathing pattern of the horse; most evidently, an exaggerated abdominal effort during expiration. Similarly, areas of consolidated

lung resulting from bacterial pneumonia will almost certainly not benefit from the delivery of antibiotics via the inhalation route.

What are the advantages and disadvantages of inhalation therapy?

The main advantage of inhalation therapy is the delivery of drug to the intended site of action; namely, the airway. Although drug delivery to the airways can readily be achieved by systemic administration, this approach results in widespread exposure of extra-pulmonary organs to the administered drug, with the potential for the induction of unwanted adverse effects. For example, the systemic administration of beta adrenergic agonist drugs, intended to relieve bronchospasm, has been associated with tachycardia, excitement and excessive sweating. Other examples include the reduction in gastrointestinal motility associated with the systemic administration of anticholinergic drugs and adrenal suppression and immunosuppression associated with the frequent systemic administration of corticosteroids. Inhaled administration of drug, directly to the targeted site of action, also has the potential to reduce drug costs, although this must be offset against the costs associated with the equipment required to administer the drug via this route. Additionally, inhaled therapy has the potential to shorten the drug withdrawal time required prior to competition in performance animals and in accordance with regulations regarding tissue residues, although specific data are very much lacking in this respect. Finally, the direct delivery of drug to the intended site of action results in a more rapid onset of action.

One principle disadvantage of inhalation therapy is the vast array of factors which influence the particle size distribution of the generated aerosol, including the properties of the aerosolised solution and the method of aerosol generation. When considered along with the variable

breathing strategies of the horse, these factors render it almost impossible to accurately predict the efficiency of drug deposition within the equine lower airways. In addition to these predicted variations, the authors have also demonstrated marked variation in both total and respirable drug (salbutamol) deposition within a standardised *in vitro* experimental model following both MDI and mesh nebuliser-generated aerosol delivery via a commercially available equine spacer device (*R.S. Pirie personal communication*). This work demonstrated an additional source of variation in drug delivery which could not be attributed to differences in drug composition, method of aerosol generation or breathing strategy, as a constant (non-tidal) airflow was maintained throughout the duration of delivery. A similar degree of variation in output has also been reported by Votion *et al* (1997) in relation to both ultrasonic nebulisation and jet aerosol delivery and by Janssens *et al* (1999) in relation to MDI delivery to children, with the magnitude of variation in the latter study being dependent on the spacer used.

Consequently, and in comparison to systemic therapy, it is difficult to develop definitively appropriate dosing strategies. Therefore, there is a general consensus that the drug should be administered largely to effect in each case, with the published recommendations being used as guidelines. Similarly, the certain variation in drug delivery, and therefore systemic absorption, between cases renders any attempt to develop reliable and reproducible drug withdrawal recommendations problematic.

In comparison to enteral or parenteral drug administration, inhalation therapy is time consuming and often necessitates several daily administrations. Furthermore, a degree of exposure of the handler and administrator to the active drug is inevitable and performing the technique in a well ventilated environment is advisable.

Available techniques for equine inhalation therapy

A variety of inhalation therapy delivery systems are available for use in the horse, some of which are custom made for equine use and some are adapted from equivalent human systems.

Mechanical nebulisation

Mechanical nebulisers have been used for many years to generate aerosols for equine inhalation therapy. Aerosols are generated either by applying airflow to draw liquid from a reservoir through a capillary tube (jet nebulisation), by vibration of a standing reservoir of liquid (ultrasonic nebulisation) or more recently by forcing the liquid through multiple apertures in a vibrating mesh (mesh nebulisation).

Jet nebulisation: For jet nebulisation, gas flows are usually generated using either a compressor (generally designed for human inhalation therapy) or a compressed gas cylinder with an appropriate regulator. As the diameter of aerosolised particles is inversely proportional to airflow, difficulty in generating sufficiently high flow rates constitutes the principal limitation of jet nebulisation, whereby a minimal air flow of 6-8L/min at the input of the jet nebuliser is required to generate an aerosol with a high particle content less than 5 micrometres in diameter (Clay et al 1983a and b). Furthermore, the equipment required for jet nebulisation can be cumbersome and expensive and the delivery of drug can be prolonged, a significant consideration when the procedure, which necessitates connection to either a mains electricity supply or compressed gas cylinder, requires continued restraint of the horse.

Ultrasonic nebulisation: Ultrasonic nebulisation has also been used in equine inhalation therapy for a number of years whereby the aerosol is generated by vibrations of a piezo-electric crystal driven by an alternating electric field. Despite the relative ease with which ultrasonic nebulisation can be applied in the field, it is generally accepted that ultrasonic nebulisation generates a wider variation in aerosolised particle sizes compared with jet nebulisation.

Mesh nebulisation: Recent developments in nebuliser technologies have resulted in the development of mesh nebulisers and an equine-specific system (Flexineb[®], Nortev Ltd, Galway, Ireland; Figure 1) is currently in common use in equine practice. Mesh systems are silent and can be battery powered, both significant advantages in relation to equine inhalation therapy. The particle size distribution within the aerosol is largely determined by the size of the apertures within the vibrating mesh and the authors recently measured the mass median aerodynamic diameter (MMAD) of aerosolised salbutamol particles generated by the Flexineb[®] system to be 1.4 micrometres, with a geometric standard deviation of 3.2 micrometres and therefore consistent with the size distribution required to penetrate the equine lower airways (*R.S. Pirie personal communication*).

Metered dose inhalers (MDIs)

MDIs are a popular alternative to mechanical nebulisers, permitting the relatively rapid administration of an aerosol with less variation in particle size. Previous studies have demonstrated superior deposition of MDI particles in the equine lung versus standard nebulisation. Furthermore, the non-requirement for electrical power constitutes an additional advantage of this method of administration. With MDIs, the active drug is either suspended or dissolved in a volatile propellant which is released through a metering valve with each manual

actuation of the device. In human inhalation therapy, due to the rapid propulsion of the aerosol, these devices require coordination between inhalation and actuation of the device to ensure effective drug delivery. The importance of adopting an optimal technique for MDI use has been emphasised in relation to both human and equine inhalation therapy, with a view to maximising the efficiency of drug delivery to the lower airways and any deviation from optimal technique is considered to adversely affect drug output (Table 1). In human medicine, correct MDI technique has generally been assessed through adherence to 7 key sequential steps; namely, shaking the MDI and removing the cap, exhaling prior to MDI use, holding the MDI upright, proper timing of actuation, slow inspiratory effort, one MDI actuation per breath, breath holding for ≥ 5 seconds. Much of the advice offered to horse owning clients has understandably been adapted from these steps, although some cannot be applied to the horse (e.g. slow inspiratory effort and breath holding). A recent study (*in press*) by the authors has critically appraised some of the recommendations often provided on the optimal use of an MDI device. With respect to the efficiency of salbutamol delivery, this study failed to demonstrate any significant detrimental effect of not shaking the MDI prior to each of multiple consecutive actuations (provided the device was shaken prior to the first actuation), not maintaining an optimal angle of MDI actuation within the spacer and performing multiple rapid actuations in rapid succession, all factors which could significantly impact on the level of compliance of the user.

Dry powder inhalers

Dry powder inhalers are breath-actuated devices which rely on the inspiratory airflow of the patient to de-aggregate the dry powder drug. Unlike the MDI, the dry powder system permits optimal coordination between inspiration and drug delivery. However, the necessity for the

generation of high inspiratory flow rates, which can be achieved voluntarily in many human patients, requires the use of a mask with an airtight seal when applied to the horse. Consequently, these systems are rarely used in equine practice.

Spacers and facemasks

Currently, equine inhalation therapy (via both nebulisation and MDIs) almost invariably involves the use of a holding chamber or spacer, either applied directly to one nostril via a flexible nose piece (e.g. EquineHaler[®], Kruuse, Sherburn in Elmet, UK [Figure 2], Aerohippus[®], Trudell Medical International, London, Ontario, Canada) or used in conjunction with a facemask (e.g. Equine Aeromask[®], Trudell Medical International, London, Ontario, Canada [Figure 3], Flexineb[®], Nortev Ltd, Galway, Ireland [Figure 1]), thus improving the characteristics of the aerosol and reducing the dependency on synchronisation with the beginning of inspiration when an MDI is used. Spacers are fitted with a series of one-way valves to facilitate inspired air to flow via the chamber and exhaled air to by-pass the chamber. In human inhalation therapy, the benefits of a spacer also include the capture of large aerosolised droplets which would otherwise deposit in the oropharynx, with the resultant risks of opportunistic oropharyngeal infections (e.g. candidiasis) and voice hoarseness. This appears to be less of a consideration in equine inhalation therapy due to the obligate nasal breathing characteristics of the horse. Spacers designed or adapted for use in infants (e.g. BabyHALER[®], GlaxoSmithKline Inc., Ontario, Canada [Figure 4a], Volumatic[®], GlaxoSmithKline Inc., Ontario, Canada [Figure 4b]) have also been successfully used in equine therapy due to the incorporation of a flexible nose piece. Although these devices offer similar advantages as equine-specific spacers at a lower cost, this has to be offset against the occasional difficulty in establishing an effective seal over the horse's nostril. An alternative system (Equine Aerosol

Drug Delivery System, 3M Animal Care Products, St. Paul, MN, USA), which consisted of a spacer designed for drug delivery directly into the horse's nostril, underwent preliminary investigation over a decade ago with some promising results in relation to comparative drug delivery (Derksen et al 1996); however, this device failed to reach the commercial market.

The accumulation of static electricity within spacers and facemasks should be avoided as this has been shown to result in a significant retention of drug within the holding chamber. Consequently, towel drying of these devices following cleaning is contraindicated; rather they should be allowed to drip dry prior to subsequent use (Table 1).

Available medications for equine inhalation therapy

A wide array of medications can be delivered by the inhaled route; however, inappropriate delivery of drugs not evaluated for inhaled administration may result in airway inflammation and/or bronchospasm. Furthermore, when applying inhaled therapy using medicines not authorised for this route of administration, care should always be taken to ensure clinical justification for this approach through adherence to the cascade and due consideration should always be applied to any associated changes in appropriate drug withdrawal times. This review will focus on medications which have been reported in the literature and which are considered appropriate for this route of administration. Such medications fall into the following categories: corticosteroids, bronchodilators, cromones and antimicrobials. Table 2 lists the medications commonly administered by MDI in equine inhalation therapy. Recommended dosages are also listed; however, as previously stated, appreciation of the numerous factors which influence drug output (e.g. delivery device, spacer, breathing pattern) and the marked variation in drug delivery even under controlled experimental conditions renders any attempts to develop

accurate dosing recommendations problematic (Table 1). This is highlighted by the marked variation in apparently efficacious MDI-generated beclomethasone dosages (ranging from 500 μ g to 3750 μ g q12h) reported in the veterinary literature. The dosage guidelines provided are mostly derived from a number of studies which assessed clinical efficacy by a variety of methods (e.g. clinical scoring and pulmonary function), primarily in severe equine asthma.

Corticosteroids

In human medicine, the use of inhaled corticosteroids has been shown to be highly beneficial in the treatment of asthma and consequently, this therapeutic approach has been adopted for the treatment of equivalent conditions in the horse; namely, severe and non-infectious mild to moderate equine asthma. The proposed benefits of the inhalation route for corticosteroid administration include the local delivery of high drug concentrations at the site of inflammation, an advantage further supported by the large number of glucocorticoid receptors within the bronchial epithelium and pulmonary vascular endothelial cells. An additional benefit of this therapeutic approach is the theoretical minimisation of systemic adverse effects including laminitis and adrenal suppression. Any systemically absorbed drug is rapidly eliminated, thus reducing drug systemic life span. However, inhaled beclomethasone has been shown to decrease plasma cortisol, indicating feedback inhibition of the adrenal gland and one study reported no difference in serum cortisol concentrations between horses with severe asthma treated with aerosolized beclomethasone (1320 μ g q12h) and those treated with intravenous (0.1mg/kg q24h) dexamethasone (Rush et al 1998). Similarly, adrenal suppression is a recognised consequence of inhaled corticosteroid therapy in humans, predominantly, but not exclusively in children and in association with high dose administration, resulting in recommendations for adrenal suppression screening in select patient groups (Sannarangappa

and Jalleh 2014). Beclomethasone dipropionate (Figure 5) and fluticasone propionate are the most commonly used corticosteroids in equine inhalation therapy, both of which are available as MDIs. Others include triamcinolone acetonide and budesonide. Fluticasone is generally regarded as a more potent corticosteroid than beclomethasone and, compared with systemic (intravenous) dexamethasone, resulted in less suppression of endogenous serum cortisol. Furthermore, long term (11 months) administration of inhaled fluticasone resulted in no significant effects on measured innate and adaptive immune parameters, thus supporting its potential use as a maintenance therapy for severe equine asthma (Dauvillier et al 2011).

Recently, anecdotal reports are emerging of the inhaled administration of nebulised dexamethasone preparations licenced for intravenous use. To the authors' knowledge, there are no published studies which have critically evaluated the efficacy or safety of this approach.

Bronchodilators

Bronchodilators relax airway smooth muscle and their use in horses is most commonly applied to cases of severe equine asthma, where they represent a form of symptomatic therapy which is applied to transiently relieve lower airway obstruction while additional environmental and pharmacological interventions are aimed at preventing and controlling the underlying airway inflammation. Additionally, bronchodilators may be used prior to other forms of inhalation therapy to maximise drug deposition within the lower airways (Rush et al 1999) and in rare cases of pulmonary oedema to reduce pulmonary water content. When used to relieve airway obstruction in clinical cases, it should be remembered that a reduction in airway calibre may result from a variety of mechanisms, including bronchospasm, mucus plugging of the airways and peribronchiolar thickening due to cellular accumulation and smooth muscle and collagen hyperplasia. Therefore, incomplete resolution of lower airway obstruction following the

administration of inhaled bronchodilators may either reflect poor drug penetration of the lower airways or a significant contribution of these latter factors to the overall airway narrowing.

Two classes of bronchodilators exist; anticholinergics and beta-2 adrenergic agonists. As bronchial smooth muscle tone is largely influenced by the parasympathetic supply, anticholinergic drugs, competitive inhibitors of acetylcholine, have been shown to be more efficacious with regard to their bronchodilatory effects. Ipratropium is the principal anticholinergic drug used in inhalation therapy which, due to its targeted deposition and poor absorption from the lung, is not generally associated with the systemic adverse effects seen with systemically administered anticholinergics (e.g atropine), including tachycardia and gastrointestinal stasis. However, reported side effects in humans include thickening of bronchial secretions, decreased mucociliary clearance and inhibition of cilia beating. Inhaled ipratropium provides effective bronchodilation for 4 to 6 hours.

Despite the superior bronchodilatory effects of anticholinergics, beta-2 adrenergic drugs are used more commonly in equine practice. This class of drug binds to the widespread beta-2 adrenoreceptors on the surface of airway smooth muscle. These include short acting (1-2 h duration) drugs such as albuterol (also termed salbutamol; Figure 6) and longer acting salmeterol (up to 12 h duration), which has a slower onset of action (15-30 min). In addition to promoting bronchodilation, beta-2 adrenergic agonist drugs enhance mucociliary clearance from the lung and have moderate anti-inflammatory effects. As anticholinergics and beta-2 agonists tend to exert their bronchodilatory effects at different levels throughout the airways, anticholinergics primarily at the larger airways and beta-2 agonists primarily in the peripheral airways, their combined use can have beneficial additive effects (Hoffman et al 1993).

Preparations containing both ipratropium and albuterol are commercially available; however, the authors have no direct experience of using these combined preparations.

Drug combinations

The use of MDIs containing a combination of both a corticosteroid and a long acting bronchodilator is becoming increasingly popular in the control of human asthma, with reports of improved symptom control as well as greater convenience. Such “combination medications” (e.g. budesonide and formoterol [Symbiocort[®], AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA], fluticasone and salmeterol [Seretide[®], GlaxoSmithKline Inc., Uxbridge, UK] beclomethasone and formoterol [Fostair[®], Cheisi Ltd., Sheadle, UK; Figure 7]) have not yet been evaluated in the horse. However, despite the increased costs associated with this approach, there may be clinical advantages to this approach during the early treatment phase of certain cases of severe equine asthma.

Antimicrobials

By avoiding the necessity to administer larger doses of systemic antimicrobials to attain adequate concentrations in the respiratory secretions, inhaled antimicrobial therapy offers some advantages over other routes of administration, including a likely reduction in the risk of systemic adverse effects. Indeed, the achievement of high and prolonged drug concentrations within the airways whilst maintaining low serum concentrations has been clearly demonstrated with various antibiotics (gentamicin and marbofloxacin) when aerosolised delivery has been compared with systemic (intravenous) administration (McKenzie et al 2000, Art et al 2007). This approach has been used in humans for a number of years, particularly aimed at the treatment or prevention of *Pseudomonas aeruginosa* colonization of the airways in cystic

fibrosis (CF), but also more recently in the treatment of non-CF bronchiectasis and ventilator-associated pneumonia. With the exception of CF treatment, the majority of inhaled antimicrobial treatments applied in human medicine continue to rely on the “off label” use of antimicrobials designed for parenteral administration. Although the presence of preservatives and the non-physiological composition of many antimicrobial preparations have the potential to render them unsuitable for inhalation therapy, there remains a limited amount of information within the literature addressing this matter. Both gentamicin (50mg/ml) and cefquinome (45mg/ml) have been administered to horses without inducing any significant airway inflammation and no detrimental effects on pulmonary function were detected following cefquinome (45mg/ml) and marbofloxacin (25mg/ml) inhalation (Art et al 2007, Art et al 2010). Despite these apparently encouraging results and the reported efficacy of this approach in equine neonatology, there is significant lack of efficacy studies in adult equine lung infections. One study on racehorses with lower airway inflammation did reveal comparable results (improvements in tracheal secretion cytology and bacteriology and rate of recurrence of bacteria isolation) when inhaled amikacin (3.3mg/kg) treatment was compared with systemic (10mg/kg) administration of the drug (Ferrucci et al 2013). It is clear that further studies are required before an objective consensus on the value of inhaled antimicrobials can be reached. However, factors other than the inflammation and bronchospasm inducing capacity of the drug also require particular consideration in relation to this therapeutic approach. Firstly, many of the conditions which may theoretically warrant the delivery of antimicrobials to the airways are also associated with severely compromised ventilation of the affected lung segment, either through consolidation, airway narrowing or the accumulation of tenacious secretions within the airways, factors which will significantly reduce the deposition of any inhaled medication. Under such circumstances, reliance on haematogenous delivery of the drug may be more effective. Secondly, careful compliance with appropriate antimicrobial stewardship policies

should be ensured. This relates primarily to the appropriateness of the antimicrobial selected, particularly in light of the variable, yet inevitable environmental and personnel exposure to the aerosolised drug during administration. Such practices have the potential to expose a wide variety of bacteria to sub-therapeutic levels of antimicrobials with the subsequent risk of promoting the selection of resistant strains.

Cromones

The administration of sodium cromoglycate to horses with severe equine asthma was first reported over 30 years ago. The mechanism of action of this treatment is not fully understood; however, it has been attributed to a local effect on nerve endings, reduced leucocyte recruitment, and stabilisation of airway mast cells, the latter effect theoretically rendering this approach more applicable to disease prophylaxis in the face of anticipated allergen exposure. Although the role of mast cells in severe equine asthma remains speculative, a sub-category of mild to moderate asthma is characterised by increased metachromatic cell ratios in the airways and the authors are aware of a renewed interest in the application of this therapeutic approach to this particular syndrome. Although no product is currently licensed for inhaled administration to horses, licenced human preparations containing cromolyn sodium have traditionally been used for equine inhalation therapy, initially via nebulisation of 2% solution and more recently via commercially available MDIs, currently available in the UK (Intal CFC-free Inhaler®). Although nedocromil sodium (Tilade®) has been used as an alternative to cromolyn sodium in the treatment of human asthma and has been proposed as a treatment for equine metachromatic mild to moderate equine asthma, there is currently no published data on its efficacy in the horse.

Miscellaneous treatments

In addition to its diuretic effects, frusemide, when administered by inhalation, has been shown to have bronchodilatory effects via incompletely understood and likely complex mechanisms (Broadstone et al 1991). Consequently, this approach has shown some efficacy in the treatment of severe equine asthma. As the process of mucus clearance from the airways is dependent on a number of factors, including mucus viscosity, mucus volume and ciliary activity, each of these have been targeted as a means of improving the efficiency of this process. With regard to inhalation therapy, the most commonly used approach is to administer aerosolised saline in an attempt to decrease the viscosity of the mucus, thus enhancing its clearance. The efficacy of such approaches remains unclear.

Summary

Inhalation therapy is now commonly used in the treatment of a variety of equine respiratory conditions with a wide variety of drugs being routinely administered via this route. Despite the many advantages associated with this therapeutic approach, there are a number of considerations which have to be applied to each case in order to determine whether this route of drug administration is applicable. Such considerations include the intended target site for drug deposition, the capability of the available inhalation delivery systems to generate aerosols with a particle size distribution pattern capable of reaching the target site, any physiological, pharmacological or pathological factors which may compromise ventilation of the target site, any potential detrimental effects of direct drug delivery to the airways or handler exposure to drug aerosols, the costs associated with the drug and/or required delivery equipment, the time constraints and commitment of the owner and the duration of anticipated treatment. Only when these considerations are made on a case-by-case basis can an opinion be reached with regard

to the suitability of this approach, which, if deemed suitable, continues to offer a valuable means of treating airway disease in the horse.

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Figure legends



Figure 1: Image depicting ultrasonic nebulisation of solubilised drug to a horse using the Flexineb® system (Nortev Ltd, Galway, Ireland). The aerosol is created by vibrations of a piezo-electric crystal driven by a battery-generated alternating electric field. The mounting of the aerosol holding chamber and the battery on the mask facilitates the administration of inhaled therapy without the necessity for continuous head restraint or close proximity to a mains power supply.



Figure 2: The EquineHaler® (Kruuse, Sherburn in Elmet, UK) spacer device, specifically designed for MDI-generated drug administration to the horse.



Figure 3: Administration of MDI-generated inhaled medication to a horse using the Equine Aeromask® system (Trudell Medical International, London, Ontario, Canada), with associated holding chamber (spacer).



Figure 4: Alternatives to equine-specific spacers include (a) the Babyhaler® and (b) the Volumatic® spacer (both GlaxoSmithKline Inc., Ontario, Canada). Although their adaptation for use in infants includes the incorporation of a flexible nose piece, compared with the equine-specific spacers, it can be more difficult to establish an appropriate seal at the nostril.



Figure 5: Beclomethasone dipropionate MDI (Clenil modulite®, Cheisi Ltd., Sheadle, UK), a commonly used product for inhaled steroid medication in the horse.



Figure 6: Salbutamol MDI, a commonly used beta-2 adrenergic agonist bronchodilator with a rapid onset but limited duration (1-2h) of action.



Figure 7: Example of an MDI product (Fostair®, Cheisi Ltd., Sheadle, UK) containing both a corticosteroid (beclomethasone) and long-acting bronchodilator (formoterol). Other corticosteroid/bronchodilator combinations are available. The use of such “combination medications” is becoming increasingly popular in the control of human asthma; however, they have not yet been objectively evaluated in the horse.

Table 1: A list of factors which will influence the efficiency of drug delivery to the lower airways.

Factor	Mechanism of influence
Properties of drug solution (jet and ultrasonic nebulisers)	<ul style="list-style-type: none"> • Viscosity, density, surface tension and hygroscopic growth potential of the solution will influence aerosolised particle diameter
Method of aerosolisation	<ul style="list-style-type: none"> • Jet and ultrasonic nebulisers generate aerosols with more variation in particle size distribution compared with MDIs
Appropriate use of device - Flow rates (jet nebulisers)	<ul style="list-style-type: none"> • When using jet nebulisers, particle size is inversely proportional to air flow rates used to generate the aerosol
Appropriate use of device - Shaking device prior to actuation (MDI)	<ul style="list-style-type: none"> • Shaking MDIs prior to use to ensures appropriate mixing of drug and propellant
Appropriate use of device - Counting total number of actuations (MDI)	<ul style="list-style-type: none"> • MDIs will continue to express propellant upon actuation even following depletion of the active drug
Appropriate use of device - Coordinating actuation with respiratory cycle (MDI)	<ul style="list-style-type: none"> • Beneficial to actuate the MDI into spacer during a period of zero, immediately prior to inhalation
Appropriate maintenance of equipment - Cleaning (ultrasonic nebulisers)	<ul style="list-style-type: none"> • Failure to adhere to manufacturer's instructions may influence the efficiency of aerosol generation
Appropriate maintenance of equipment - Extended and repeated use of disposable nebuliser cups (jet nebulisers)	<ul style="list-style-type: none"> • Re-use of disposable nebuliser cups, not intended for extended use, will reduce the respirable particle fraction of the aerosol
Appropriate maintenance of equipment - Drying of spacers and facemasks	<ul style="list-style-type: none"> • Towel drying of facemasks and spacers has the potential to result in sufficient static electricity accumulation to significantly attract aerosolised particles, thus preventing their passage into the airway. Drip drying of this equipment is advisable.
Efficiency of lung ventilation	<ul style="list-style-type: none"> • Various physiological or pathological factors will influence ventilation of different lung segments. Examples include drug- or disease-associated bronchospasm, lung consolidation/atalectasis, mucus plugging
Breathing strategy of horse	<ul style="list-style-type: none"> • Any deviation from a perceived optimal breathing pattern (slow inhalation followed by a period of zero flow) will impact on the efficiency of delivery. Examples include short rapid respirations and prolonged periods of breath holding
Random variation in drug output from device (nebulisers and MDIs)	<ul style="list-style-type: none"> • There is marked variation in drug output from MDIs (between actuations) and nebulisers (between treatment periods), which appear to be independent of the above factors.

Table 2: A selection of drugs available as MDIs commonly used in equine inhalation therapy. These products are all unlicensed for use in the horse and the dosing regimens provided are suggestions only. Consideration should be given to the various factors which may influence drug delivery to the lower airways and the variation in drug output from the devices (see Table 1).

Drug class / active component	Tradename examples	Dose	Dose per actuation	Actuations per 500kg horse	Frequency
Corticosteroids					
Beclomethasone dipropionate	Clenil modulite [®]	1 to 5 µg/kg	250 µg	2 to 10	q 12h
Fluticasone propionate	Flixotide [®]	2 to 4 µg/kg	250 µg	4 to 8	q 12h
Anticholinergics					
Ipratropium bromide	Atrovent [®]	0.4 to 0.8 µg/kg	40 µg	5 to 10	q 4 to 6h
Beta-2 adrenergic agonists					
Salbutamol	Ventolin [®]	2 µg/kg	100 µg	10	q 2 to 4h
Salmeterol	Serevent [®]	0.5 µg/kg	25 µg	10	q 12h
Combination drugs					
Salmeterol and fluticasone	Seretide [®]	0.2 to 0.4 µg/kg * 2 to 4 µg/kg *	25 µg * 250 µg *	4 to 8 *	q 12h
Formoterol and beclomethasone	Fostair [®]	0.06 to 0.18 µg/kg * 1 to 3 µg/kg *	6 µg * 100 µg *	5 to 15 *	q 12h
Chromones					
Sodium cromoglicate	Intal CFC-free [®]	0.04 to 0.06 mg/kg *	5 mg	4 to 6 *	q 6-12h

* Calculated doses extrapolated from a combination of anecdotal evidence of efficacy, equivalent human dosing regimens and recommended doses of individual components in horses (combination therapy).