Inhalation therapy in horses

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Introduction

Inhalation therapy refers to the administration of aerosols into the airway, allowing rapid deposition of a high concentration of medication in the airways, and minimizing systemic side effects. The efficacy of inhalatory therapy is influenced by a great number of factors, like the design of the device and the physical characteristics of the drug solution, which includes size, hydrophobicity and shape. Two main parameters are generally used to evaluate the performance of nebulizers: the droplet size distribution of the aerosol and the drug output rate. The droplet size is the most relevant characteristic of aerosol therapy. Ideally, particles of 1-5 um are deposited in small diameter bronchioles and in alveolar acini by gravitational sedimentation. Particles smaller than that (less than 1 μm) tend to remain in suspension, and just 50% are deposited in the alveoli and the other 50% is exhaled. Larger particles (>10um) are deposited in the upper respiratory tract or in larger airways and do not effectively reach the lower airways. Mid-sized particles (10-6 um) deposit in the larynx, trachea, bronchi, and large-caliber bronchioles.

There are also patient factors that can influence aerosol particle deposition including the depth of breathing, airway patency, and reactivity, bronchospasm, and coughing. There are different forms of medications that can be administered via inhalation, like solutions, powders, vapors, or pressurized cartridges (when solutions or powders are administered with a propellant). It is also important to know that the onset of action is relatively rapid, and the effects are usually short lived, because the aerosolized drugs are partially degraded in the lung, cleared from the respiratory tract by the mucociliary escalator, and absorbed into the blood stream where they followed the rest of the course as a systemic drug. Some of the medications used are mucolytics, bronchodilators, anti-inflammatories, antimicrobials, and currently, antifungals are being studied.

Forms of drug delivery

There are two forms of delivering drugs via the inhalatory route, nebulizers (jet nebulizers, ultrasonic nebulizers and vaporizers) and pressurized metered dose inhalers (pMDIs). Nebulizers are used to deliver medications formulated as a liquid, either as a solution or suspension.

Jet nebulizers work by drawing up liquid and producing a spray, which breaks up the liquid into small particles. They are economical, however, they provide a slow delivery rate, making the particle size highly variable, and require large volumes of liquid for a small amount of actual delivery. Also, they are loud. The airflow rate is important, as if it is too slow, there's an increase in droplet size, whereas if the flow rate is too fast, turbulent flow favors pharyngeal deposition and the droplets don't reach the lower airways.

Ultrasonic or "mesh" nebulizers produce a cloud of mist by using piezoelectric crystal vibrations to nebulize a pool of liquid. The frequency of the vibration is what determines the particle size, therefore higher frequencies create smaller droplets. Several factors can determine the droplet size and deposition like individual drug characteristics, nebulizer specifications, and tubing diameter and length. Compared to other nebulizers, the ultrasonic nebulizer has a faster delivery and produce more specific droplet size. Their disadvantage is that their cost is higher, and they generate heat, which may degrade the medication. The ultrasonic nebulizer available for use in horses is the Flexineb Equine Nebulizer. See fig. 2.

Vaporizers deliver the drug vaporized in steam and are considered the older forms of inhalation therapy. One major disadvantage with this type of nebulization is that the particle size and drug

deposition are highly variable. Thus, they are currently used primarily to increase the fluidity of airway secretions and therefore, favoring the elimination of mucus by the ciliary escalator and coughing.

Pressurized metered dose inhalers ensure administration of an accurate amount of medication by delivering a set amount of drug per "puff". However, there can still be some variability of drug delivery with this method. Inadequately shaking of the pMDI before use is a common source of this variability. It is also important to coordinate actuation of the device with inhalation for successful delivery. For this reason, a spacer is required in the delivery device for use in horses, and they were also modified for nasal delivery. The type of propellant influences the relative deposition of drug in the lung; hydrofluoroalkane (HFA) propellant is the only available in the United States. There are several products used as spaced devices in horses, which can be single nostril and entire muzzle masks. The single nostril masks for horses include the Equine Haler and the AeroHippus (See fig.1). The aerosol particles are suspended in the spacer, which contains a one way valve that allows flow of medication on inspiration. The commercial entire muzzle mask available is the Flexineb Equine Nebulizer, which can also be used with pMDIs.

Fig. 1. AeroHippus Equine Aerosol Chamber

Fig. 2. Flexineb Equine Nebulizer

Medications used for inhalatory therapy

The airway epithelial lining fluid absorbs drugs in aqueous forms. If delay in absorption occurs, this might result in mucociliary clearance of the drug before it has the chance to achieve full effect. Medications administered into the airway can be systemically absorbed through alveolar capillaries into the bloodstream. Something to be considered when designing the therapy is that, physiologic changes in the lungs, like age-related changes or pathologic conditions as a result of the disease process, may decrease the effectiveness of inhalation therapy. When designing the therapeutic plan, it must be having in mind an appropriate duration of treatment and frequency of administration. Viscous substances take longer to nebulize and have longer droplet size; and larger droplets get aerosolized faster.

Mucolytic drugs

Excessive mucus results from increased production due to inflammation or decreased clearance, can be detrimental altering gas exchange properties and retaining harmful substances or bacteria within the respiratory tract. Physiologic saline exerts mucolytic activity when applied topically to respiratory mucus. This can help to breakdown the oligosaccharide cross-linking and reduce the viscosity of mucus making it easier to clear. Other mucokinetic agents that can be administered by inhalation include hygroscopic agents like propylene glycol, or true mucolytics like acetylcysteine.

Bronchodilators

Beta-2-adrenergic agonists are sympathomimetic drugs that inhibit smooth muscle contraction by decreasing intracellular calcium stores and the activity of smooth muscle cell protein kinase, thus, leading to bronchodilation. There are short-acting and long-acting beta-2 agonists. The Short-acting ones have a quick onset of action, within 5 to 15 minutes, duration as short as 2 to 4 hours, and are the most effective drugs for emergency situations of acute bronchoconstriction in patients with asthma, or in diseases associated with smooth muscle hypertrophy, hyperplasia, or metaplasia that are particularly prone to the occurrence of life-threatening bronchoconstriction. Some of the drugs used are: albuterol (salbutamol) and levalbuterol. Long-acting beta-2 agonists have a slower onset time of 30 minutes, with a peak activity at 3 hours, and duration of 8 hours. Salmeterol is one of the drugs of this group. Systemic side effects include trembling, sweating, tachycardia, and cardiac arrhythmia. This group of drugs help to reestablish normal gas exchange and comfort, and can also aid in improve the delivery of inhalation corticosteroids or other therapies, but does not treat the underlying disease.

Muscarinic cholinergic antagonists are parasympatholytic drugs that work similar to atropine, blocking muscarinic receptors and resulting in inhibition of calcium release from myocytes, thus preventing contraction of airway smooth muscles. They are very potent inhibitors of broncho-constrictions. Some possible side effects, though uncommon, include decreased salivation, tachycardia, mydriasis, and decreased gastrointestinal motility. They have a slow onset of action, 30 to 60 minutes. The only formulation recommended for use in the horse is ipratropium.

Nitric oxide (NO) binds to guanylyl cyclase and therefore increasing its activity to increase production of cyclic guanosine 3’5’-monophosphate (cGMP). cGMP then acts on smooth muscle, causing vasodilation and bronchodilation. Thus, it can be used as a therapy in acute respiratory distress syndrome and pulmonary hypertension. It may even play a role in mast cell stabilization. It is important to remember that NO in large amount can be toxic because of the formation of nitrite and peroxynitrite radicals, which can cause increased airway responsiveness.

Inhalatory bronchodilators used in horses		
Type of bronchodilator	**Drug**	**Dosage**
Short-acting beta2 adrenergic agonists	Albuterol (Salbutamol)	1-2 µg/kg, q 1-4h
	Levalbuterol	0.5 µg/kg, q 4h
Long-acting beta2 adrenergic agonists	Salmeterol	0.25-1.0 µg/kg, q 6-8h
Muscarinic cholinergic antagonist	Ipratropium	1-3 µg/kg, q 6-8h

Anti-inflammatories

Mast cell stabilizers inhibit mast cell degranulation and thus preventing the release of several mediators of inflammation, including prostaglandins, leukotrienes and histamine by blocking calcium channels. They inhibit bronchoconstriction by means of decreasing the inflammatory cascade. They are considered prophylactic or preventative, and for the best results, they require a period of 1 to 2 weeks of steady use before the onset of signs. It is mainly indicated in horses with seasonally recurrent asthma, and when a high percentage of mast cells is present in the bronchoalveolar fluid cytology. Formulations available include nedocromil (Tilade) and cromoglycate (Intal).

Corticosteroids: bind to intracellular glucocorticoid receptors leading to inhibition of nuclear factor-kβ and ultimate downregulation of the gene expression of inflammatory cytokines. There are several side effects associated with systemic administration like gastrointestinal ulceration, laminitis,

immunosuppression, and others. In cases of long-term treatment with corticosteroids for horses with asthma, inhalatory therapy has become very popular as the adverse effects are significantly less likely. The limiting factor of the inhaled corticosteroids is their cost. Formulations of pMDI currently available include beclomethasone, fluticasone and flunisolide. Fluticasone has better potency, less systemic absorption, and a longer half-life than beclomethasone, however, the disadvantage of fluticasone is the increased cost. With beclomethasone, there has been mild respiratory infections reported in horses. There are no published data for flunisolide in horses.

Inhalatory anti-inflammatories used in horses		
Type of anti-inflammatory	**Drug**	**Dosage**
Corticosteroids	Beclomethasone: HFA	2-8 µg/kg, q 12h
	Fluticasone: HFA	2-4 µg/kg, q 12h
	Flunisolide: HFA	1-4 µg/kg, q 8h
Mast cell stabilizer	Nedocromil: CFC free	8-14 mg/500kg, q 4-8h
	Cromoglycate: CFC free	10-15 mg/500kg q 4-8h

Antimicrobials

There are several options of antimicrobials available for inhaled administration in humans. The majority are systemic formulations that have been proven to be effective when given nebulized. The selection of an antimicrobial for use as inhalation therapy should be made with care, as some drug formulations contain preservatives or stabilizers that could be harmful if inhaled. The use of sterile water as a diluent should be avoided because hypo-tonicity of the solution can cause bronchoconstriction, therefore they should be reconstituted in saline instead. Hyper-osmolality can also induce bronchial irritation. In horses, there are a few studies about inhalatory therapy using systemic formulations, however, the use is off-label. Inhalation allows delivery of antibiotics that are not well absorbed orally, and also reduces the systemic side effects. The antimicrobials studied for inhalation therapy in horses are: gentamicin, ceftiofur sodium (Naxcel), and cefquinome.

Inhalatory antimicrobials studied to use in horses			
Type of antimicrobial	**Delivery method**	**Volume of injectable and diluent**	**Dosage**
Gentamicin	Ultrasonic nebulizer	Gentamicin diluted to 50mg/mL using sterile saline	20 mL total vol. of diluted solution per adult horse q 24h (2mg/kg/day)
Ceftiofur (Naxcel)	Nebulized - Flexineb mask	Diluted with sterile water to a concentration of 50mg/mL	2.2 mg/kg q24h (or 1.1 mg/kg q12h)
Cefquinome	Jet nebulizer	5 mL injectable cefquinome + 2.5 ml saline	0.5 mg/kg q24h

Antifungals

Current clinical evidence for the use of aerosolized delivery in preventing fungal infections is limited to amphotericin B, although, itraconazole, voriconazole, and caspofungin are under investigation, in humans. There are no published studies performed in horses.

Advantages and disadvantages of inhalatory therapy

Advantages

- Direct delivery of the medication in the diseased area, increasing in situ bioavailability.
- Decrease systemic side effects of the administered drug. Avoids degradation in the gastrointestinal tract and liver, and allows the use of drugs that are not bioavailable when administered orally.
- Lower doses needed. The blood-bronchial barrier limits the access of systemically administered drugs to the airway lumen and to the cells lining the lower respiratory tract, therefore, to achieve drug penetration, high systemic doses are often required.
- Onset of action is rapid.

Disadvantages

- Drug deposition varies depending on the drug used, thus the determination of half-life of inhaled drugs is difficult.
- Inhaled drugs tend to have a shorter duration of effect than when administered through the systemic route, and so more frequent administration may be necessary to obtain the desired effect.
- Some inhalatory drugs can have increased costs compared to the drugs administered systemically.

References

1. Cha, M. L. and L. R. Costa (2017). "Inhalation Therapy in Horses." Veterinary Clinics: Equine Practice **33**(1): 29-46.
2. Duvivier, D. H., et al. (1997). "Aerosol therapy in the equine species." Veterinary Journal **154**(3): 189-202.
3. Fultz, L., et al. (2015). "Pulmonary pharmacokinetics of desfuroylceftiofur acetamide after nebulisation or intramuscular administration of ceftiofur sodium to weanling foals." Equine veterinary journal **47**(4): 473-477.
4. Hoffman, A. M. (1997). "Inhaled Medications and Bronchodilator Usage in the Horse." Veterinary Clinics of North America: Equine Practice **13**(3): 519-530.
5. Le Brun, P. P., et al. (2000). "A review of the technical aspects of drug nebulization." Pharmacy World and Science **22**(3): 75-81.
6. Le, J. and D. S. Schiller (2010). "Aerosolized delivery of antifungal agents." Current fungal infection reports **4**(2): 96-102.
7. McKenzie, H. C., 3rd and M. J. Murray (2004). "Concentrations of gentamicin in serum and bronchial lavage fluid after once-daily aerosol administration to horses for seven days." American Journal of Veterinary Research **65**(2): 173-178.
8. Newman, S. P. (1985). "Aerosol deposition considerations in inhalation therapy." Chest **88**(2 Suppl): 152s-160s.