Comparative efficacy of inhaled albuterol between two hand-held delivery devices in horses with recurrent airway obstruction

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Summary

Reasons for performing study: Studies investigating the clinical efficacy of albuterol administered with the same propellant and commercially available delivery devices in horses with recurrent airway obstruction (RAO) are not currently available.

Objectives: To determine the efficacy of aerosolised albuterol administered to horses with RAO by means of 2 commercially available, hand-held delivery devices.

Methods: Ten horses with RAO were kept in a dusty environment and fed mouldy hay to induce airway obstruction. Lung mechanics were measured before and after the procedure. ΔP\text{max} was measured 5 min after administration of 180 μg of albuterol from a pressurised metered dose inhaler, using an aerosol delivery device chosen randomly. This process was repeated every 5 min until maximal bronchodilation was achieved. After a 24 h washout period, lung mechanics data were again collected using the other aerosol delivery device.

Results: Aerosolised albuterol induced a significant and rapid bronchodilation in the horses using both aerosol delivery devices. No statistically significant difference in pulmonary function was observed in response to albuterol therapy between the 2 devices. The dose required to achieve 50% of maximal bronchodilatation was not statistically different between the 2 devices (173.35 ± 78.35 μg with Device 1 and 228.49 ± 144.99 μg with Device 2, P = 0.26). The decrease in lung resistance tended to be more pronounced after albuterol administration with Device 1 (P = 0.066).

Conclusions: Aerosolised albuterol is an effective bronchodilator in horses with recurrent airway obstruction. There is no statistically significant difference between the 2 commercially available aerosol delivery devices in terms of efficacy.

Potential relevance: Aerosolised albuterol is effectively delivered using currently available devices leading to maximal bronchodilatation in horses with RAO at an average dose of 540 μg.

Abbreviations

C_{dyn}: Dynamic lung compliance
ΔP\text{max}: Maximum change in transpulmonary pressure
pMDI: Pressurised metered-dose inhaler
RAO: Recurrent airway obstruction
R\text{l}: Pulmonary resistance.

Introduction

Recurrent airway obstruction (RAO) is the most frequent cause of chronic respiratory tract disease in horses (Hotchkiss et al. 2007a), characterised by airway inflammation and bronchospasm with phases of remission when a horse’s environment is improved (Robinson et al. 1996). During disease exacerbation, bronchoconstriction, airway wall oedema and accumulation of mucus result in obstruction of the distal airways. These mechanisms induce functional changes: maximum change in transpulmonary pressure (ΔP\text{max}) increases, pulmonary resistance (R\text{l}) increases and dynamic lung compliance (C_{dyn}) decreases (Gillespie et al. 1966; Couëtil et al. 2001). Recurrent airway obstruction is believed to be an allergic reaction to organic dusts and has many similarities with human asthma (Ghio et al. 2006; Marti et al. 2008).

Inhaled short-acting β2-receptor agonists are the most effective medication for relieving acute bronchospasm (Anon 2007). Albuterol is the most commonly prescribed medication for asthma in man worldwide (Kelly 2005). Short-acting β2-receptor agonists, amongst other actions, mediate vasodilation and bronchodilation (Weiss et al. 2006). In human medicine, nebulisers and spacer devices are popular means of delivering aerosols. Small volume spacers, composed of a mouth piece and holding chamber with valves, have been developed for patients such as infants to avoid having to precisely coordinate actuation of the pressurised metered-dose inhaler (pMDI) and inhalation. Spacers have been shown to be clinically effective and result in fewer side effects from medication residue in the oral cavity (Clarke et al. 1993). Aerosol delivery to infants is more efficient from a pMDI via a small
volume spacer than from a nebuliser (Wildhaber et al. 1997). In equine medicine, various aerosolised drugs have been used successfully for the treatment of RAO (Rush et al. 1998; Derksen et al. 1999; Couëtil et al. 2005). Aerosolised bronchodilators administered with pMDI are effective and associated with minimal side effects. In particular, aerosolised albuterol has been shown to be a valuable bronchodilator with rapid onset in the treatment of RAO (Derksen et al. 1999; Rush et al. 1999). This type of therapy requires specialised devices to optimise drug delivery in the equine lung. Convenient delivery devices have been described in horses (Tesarowski et al. 1994; Derksen et al. 1996). Some of these devices use a nose piece, which fits inside the horse’s nose, instead of a face mask to deliver a known dose of any given drug from a pMDI into the equine lung (Derksen et al. 1996). The relative percentage of a drug deposited in the lung varies based on the device used and the type of propellant. However, data on the efficacy of inhaled albuterol using available delivery devices are not available. Currently, 2 aerosol delivery devices that do not require a face mask are commercially available. A study using delivery Device 1 (AeroHippus) found that 18.2 ± 9.3% of administered beclomethasone dipropionate with hydrofluoroalkane (HFA) propellant is deposited in the lung (Hoffman et al. 2008). Another study, using delivery Device 2 (Equine Haler), reports that 8.2 ± 5.2% of administered fluticasone propionate with chlorofluorocarbons (CFC) propellant is deposited in the equine lung (Funch-Nielsen et al. 2001). These 2 studies focused on lung deposition exploring 2 different drugs administered with 2 different propellants. In human medicine, it has been demonstrated that the choice of a propellant considerably influences lung deposition (Leach et al. 1998; Harrison 2002). However, CFCs have been banned from albuterol pMDI since 2008 in most countries and replaced by HFA. Studies investigating the clinical efficacy of albuterol administered with the same propellant and the commercially available delivery devices in horses with RAO are not currently available.

The purpose of this study was to evaluate if aerosolised albuterol administered to horses with RAO using aerosol delivery devices currently commercially available have comparable efficacy on lung function and to provide clinicians with guidelines for the selection of an aerosol delivery device.

Materials and methods

Horses

Ten horses (5 mares and 5 geldings), age 7–29 years, with inducible and reversible airway obstruction that are part of the RAO-affected herd belonging to Purdue University were used in the study. All horses had been housed on pasture and fed a pelleted diet for at least 3 months to ensure remission from disease. At the beginning of the study, abnormalities were not detected during physical examination of the horses. The horses were then exposed to a dusty environment by housing them in a barn and placing mouldy hay and straw in their stall. In addition, mouldy hay was shaken twice a day for 5 min next to the horses’ nose in order to increase dust exposure. People shaking hay were protected from inhalation of dust by wearing an N95 face mask. The horses remained in the confined environment until they developed clinical signs of RAO. Clinical scores were assigned to each horse once daily by use of a scale adapted from Tesarowski et al. (1996) to screen for the onset of airway obstruction. The scale ranges from 0–21 and a clinical score of ≥12 was considered sufficient to warrant lung function testing. For inclusion in the study, a maximum change in transpulmonary pressure (ΔP_{Lmax}) ≥15 cmH₂O was required after the induction period. If that pressure was achieved, lung mechanics were measured at baseline and the horse was enrolled in the treatment trial using one of 2 aerosol delivery devices chosen at random. The horse then returned to its stall in the dusty environment for a minimum of 24 h washout period. The following day, if the horse met the inclusion criteria, lung mechanics data were again collected using the other aerosol delivery device. If the criteria were not met, the horse was maintained in the dusty environment until inclusion criteria were met. This protocol was approved by the Purdue Animal Care and Use Committee. Horses were to be removed from the study if they became anorectic for >24 h.

Aerosol delivery devices

Two aerosol delivery devices, both commercially available, referred to as Devices 1 and 2 (Fig 1), were used for albuterol administration using a pMDI and HFA propellant. Both devices are hand-held chambers connected to a nose mask which is placed over one nostril. The pMDI was inserted into the back piece of the chamber where the breathable particles were suspended until the horse breathed them through a one-way valve. The device was held on the nostril for 3 respiratory cycles to ensure complete inhalation of the dose. The breathing chamber of Device 1 was a cylinder whereas the breathing chamber of Device 2 was an ellipsoid.

Lung mechanics

Oesophageal pressure was measured using a balloon catheter (internal diameter 4.8 mm; outside diameter 6.4 mm; 240 cm in length), which was advanced to the mid-thoracic region and connected to a pressure transducer. The balloon was a condom taped around the catheter tip and inflated with 3 ml of air. The position of the balloon was recorded for each horse at the time of baseline testing prior to induction of RAO exacerbation and used subsequently for all lung mechanics tests. Transpulmonary pressure was defined as the difference between oesophageal pressure and atmospheric or mask pressure, depending on whether the horse was fitted with a facemask or not. When measuring

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airflow, a mask was fitted around the horse’s nose with a pneumotachometer coupled to a pressure transducer that generated a signal proportional to airflow. Output signals were recorded by computer software as previously reported (Couëtil et al. 2001). At least 10 respiratory cycles from breaths devoid of artefacts were selected for analysis.

For each trial, baseline measurements of lung mechanics including airflow, change in transpulmonary pressure (ΔPLmax) were recorded. Values for resistance (RL) and compliance (Cdyn) were computed in accordance with the method described by Amdur and Mead (1958). The mask was then removed and another baseline ΔPLmax measured. The horse was then given 2 puffs (180 μg) of albuterol (Ventolin) using one of the 2 delivery devices and ΔPLmax was measured again 5 min later. This process was repeated until maximal bronchodilatation was achieved (≤10% difference between 2 consecutive doses) or a maximum of 10 puffs had been administered. After the last measurement, the mask was replaced and lung mechanics measured again. A dose-response-curve was constructed by plotting ΔPLmax vs. albuterol dose.

Calibration of flow and pressure transducers was performed once a day before each experiment using a 3 l calibrated syringe and a water manometer, respectively.

Statistical analysis

Mean ± s.d. were calculated for data that followed normal distribution and median (range) for data with non-normal distribution. Comparison of normally distributed data between treatment groups (Device 1 vs. Device 2) was made using a paired t test. Other data were compared using a Wilcoxon signed rank test. In particular, the albuterol dose that resulted in a 50% and maximum decrease in ΔPLmax from baseline and absolute and relative difference in RL before and after the last dose of albuterol were compared between the 2 aerosol delivery devices. Changes in lung function variables (ΔPLmax, RL, Cdyn) between baseline and at the time of maximal bronchodilatation were compared between treatment groups (Device 1 vs. Device 2) using repeated measures ANOVA. Post hoc tests were used when appropriate. Significance was defined as P<0.05.

Results

All the horses met the inclusion criteria within 3 weeks of exposure to the dusty environment. The median clinical score before lung function test was 16/21 (9–19). Lung mechanics (ΔPLmax, RL and Cdyn) before administration of albuterol were not statistically different between the 2 treatment trials (P=0.51, P=0.88, P=0.79, respectively). Lung mechanics (ΔPLmax, RL and Cdyn), after the maximum effect on ΔPLmax was reached by administration of albuterol with either spacer, were not statistically different (P=0.27, P=0.20, P=0.46, respectively; Table 1).

Albuterol administered by both delivery devices induced a significant decrease in ΔPLmax (P<0.001), a significant increase in Cdyn (P<0.001) and a significant decrease in RL (P<0.001). Albuterol administered by both delivery devices induced a dose-dependent response and the responses were not statistically different between devices (P=0.26; Fig 2). There was no statistical difference between the maximal reduction of ΔPLmax observed with albuterol administered with either mask, either in absolute value (P=0.44) or in percentage of reduction (P=0.39; Fig 3). The mean dose required to reach the plateau effect was 540 μg (6 puffs). No significant further reduction of mean ΔPLmax was observed by increasing the dose beyond 540 μg. However, the response was very variable from one horse to another. Among the 20 tests performed, maximum reduction of ΔPLmax was achieved after 2 puffs in 4 tests (3 with Device 1 and one with Device 2), after 4 puffs in 2 tests (one with each device), after 6 puffs in 8 tests (2 with Device 1 and 6 with Device 2), after 8 puffs in 4 tests (all with Device 1) and after 10 puffs in 2 tests (all with Device 2).

The absolute and relative reduction in RL following administration of the last albuterol dose tended to be higher with Device 1 (1.10 [-0.07–3.31] cmH2O/l/s; 65.1 [7.9–89.0]%); P=0.066) than with Device 2 (0.68 [0.61–1.99] cmH2O/l/s; 53.7 [20.0–79.1]%). The absolute decrease in RL post albuterol challenge was greater with Device 1 in 6 horses but greater with

![Graph](image_url)
Device 2 in 2 horses. In one horse R
administration with both devices and R
measurement was unavailable pre-albuterol in one horse.

The dose of albuterol required to reach 50% of the maximum effect on ΔP
max was not statistically different between Device 1 (173.35 ± 78.35 μg) and Device 2 (228.49 ± 144.99 μg, P = 0.31; Fig 4).

Discussion

The 10 horses completed the study protocol and they inhaled the medication with ease. They did not exhibit any adverse effects of β2-agonist therapy and no horse exhibited anorexia throughout the study duration.

During exposure, the 10 horses exhibited clinical signs of RAO and experienced altered ΔPmax, Rl and Cdyn as previously reported (Tesarowski et al. 1996; Rush et al. 1998; Derksen et al. 1999). Administration of albuterol significantly improved pulmonary function parameters in all the tested horses. These findings are consistent with published studies (Derksen et al. 1999; Rush et al. 1999).

No statistically significant difference was noted in ΔPmax, Rl and Cdyn before the treatment trial using delivery device. These results indicate that a 24 h washout period between the 2 trials was adequate and are consistent with the fact that during exacerbation of the disease, a horse’s pulmonary function remains relatively stable (Jean et al. 1999).

All doses of albuterol induced a significant decrease in ΔPmax within 5 min of administration, which indicates a rapid improvement of airway obstruction. These results are similar to those reported using fenoterol (Tesarowski et al. 1994) and albuterol (Derksen et al. 1999; Rush et al. 1999) delivered by pMDIs combined with other delivery devices. However, in this study, the mean dose required to reach the plateau effect was 540 μg (6 puffs). No significant further bronchodilation was observed by increasing the dose beyond 540 μg. This dose is higher than the dose of 360 μg previously reported (Derksen et al. 1999). Since the same HFA propellant was used in both studies, the difference may be explained by the higher percentage of drug deposited in the lungs using the device that is no longer commercially available.

No statistically significant difference was noted in ΔPmax, Rl and Cdyn after the treatment trial using either delivery device. These results suggest that the 2 devices achieved a similar amount of drug deposition in the lungs. Data variability post-albuterol administration was higher with Device 2 than with Device 1 especially for ΔPmax (Table 1). The large standard deviation in ΔPmax post-albuterol for Device 2 is mainly due to one horse, which responded poorly to treatment with Device 2 (ΔPmax = 65.7 cmH2O at baseline and ΔPmax = 47.5 cmH2O after 10 puffs) but responded well to treatment administered with Device 1 (ΔPmax = 45.9 cmH2O at baseline and ΔPmax = 7.1 cmH2O after 10 puffs). Data analysis was repeated after excluding data from this horse and results indicated that post-albuterol ΔPmax = 14.0 ± 6.5 cmH2O with Device 2. Previous studies reported lung deposition of 18.2 ± 9.3% and 8.2 ± 5.2% using Devices 1 and 2, respectively (Funch-Nielsen et al. 2001; Hoffman et al. 2008). These results should be interpreted with caution because the studies were not peer-reviewed. Nevertheless, based on these data we would expect the dose of albuterol required to achieve 50% of the maximum effect on ΔPmax with Device 1 to be approximately half that required with Device 2. In fact, the dose required with Device 1 was only 24% lower and that difference was not statistically significant. The higher lung deposition reported with Device 1 was obtained with beclomethasone dipropionate and an HFA propellant while the lower deposition was with fluticasone propionate and a CFC propellant (Funch-Nielsen et al. 2001; Hoffman et al. 2008). Human clinical trials indicate that relative drug deposition in the lungs is approximately 2-fold higher with HFA than with CFC propellant for drugs such as beclomethasone and flunisolide (Richards et al. 2001; Harrison 2002). Therefore, lung deposition of beclomethasone-HFA in horse’s lungs using Device 2 would be expected to be around 16.4% which is similar to the 18.2% reported for Device 1 delivering the same drug formulation. This extrapolation is consistent with the present study findings.

The study revealed that albuterol delivered with Device 1 resulted in a 34% greater improvement in Rl than with Device 2 but this difference did not reach statistical significance. Conducting additional studies with a larger number of horses would be helpful to confirm if the 2 devices achieve significantly different drug delivery levels and require different dose recommendation for the treatment of RAO.

Pulmonary function is traditionally quantified using ΔPmax, Rl and Cdyn. In this study, only ΔPmax has been measured between individual administrations of albuterol. In other reports, ΔPmax and Rl appeared to be the most sensitive markers of improved airway obstruction in horses with RAO (Robinson et al. 1993; Tesarowski et al. 1994; Derksen et al. 1996; Rush et al. 1998). Measurement of ΔPmax does not require a mask fitted around the horse’s nose with a pneumotachometer coupled to a pressure transducer. However, ΔPmax is also influenced by voluntary breathing efforts and may vary with excitement or tachypnoea. In this study, Rl was also measured before and after the last dose of albuterol confirming the fact that improvement in lung function was due to reduced airway obstruction and not just changes in breathing strategy.

Bronchodilation induced by albuterol lasts for 30–60 min (Derksen et al. 1999). During the study we chose to administer albuterol 2 puffs at a time in order to reduce the time elapsed between the first administration of albuterol and the last measurement. Using this method, the time required to administer the maximal dose (900 μg or 10 puffs) and perform the last measurement was 32 min on average. If the mask were repositioned to perform a complete measurement of the lung function between each administration, the incremental dose-response curve would not have been accurate for the last
measurements. Using this protocol, it was considered that the bronchodilator effect induced by the first administration of albuterol was still present when the last measurement of pulmonary function was performed. This assumption was reinforced by the fact that $ΔP_{Lmax}$ either continued to decrease or reached a plateau as increasing dosages were delivered but it never increased by the time the last dose was administered.

A large variation was observed between horses. Some horses reached maximal bronchodilation with as little as 2 puffs (180 μg) while others required 10 (900 μg). Also, most of the improvement in $ΔP_{Lmax}$ was seen within the first few puffs after which the effect levelled off. As reported in other studies (Derksen et al. 1996), small airways of horses with RAO are occluded by mucus, airway wall thickening and bronchospasm, thus resulting in unpredictable amount of inhaled drug deposition. Furthermore, horses did not reach the same clinical score or degree of airway obstruction based on lung function testing. It is likely that some horses were more affected and therefore produced more mucus and experienced more severe bronchospasm resulting in decreased lung deposition of albuterol. However, all the horses had an improved lung function test after repeated administration, possibly because an initial bronchodilation aided drug deposition during the subsequent administration.

According to the third Expert Panel Report on Diagnosis and Management of Asthma (Anon 2007), short-acting β2-agonists are the most effective medication for relieving acute bronchospasm; however, increasing the use of short-acting β2-agonists treatment or using short-acting β2-agonists >2 days/week for symptom relief indicates an inadequate control of asthma in addition to the need for initiating or intensifying anti-inflammatory therapy. Similarly in horses, the use of short-acting β2-agonists such as albuterol is only recommended as rescue medication, as a diagnostic test for RAO or as therapy in combination with inhaled corticosteroids. In addition, the emphasis should be placed on the need to improve the environment of a horse affected by RAO by limiting antigen inhalation, particularly thermophilic moulds and actinomycetes that grow in mouldy hay (Robinson et al. 1996; Hotchkiss et al. 2007b).

In conclusion, aerosolised albuterol from a pMDI administered with either of 2 commercially available delivery devices is an effective bronchodilator in horses experiencing RAO crises. However, the primary therapy for horses affected by RAO should focus on managing and controlling their environment.

Conflict of interest

The authors declare no conflict of interest.

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Manufacturers’ addresses

1Trudell Medical International, London, Ontario, Canada.
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