The Veterinary Journal 222 (2017) 22–28

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Effects of sedation and salbutamol administration on hyperpnoea and tidal breathing spirometry in healthy horses

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ARTICLE INFO

Article history:
Accepted 5 March 2017

Keywords:
Acetylpromazine
Horse
Lung function
Respiratory disease
Salbutamol
Xylazine

ABSTRACT

Sedation is often required to perform pulmonary function testing (PFT) in horses, but drug effects may influence respiratory function. The current study was designed to characterise the effects of sedation and bronchodilator administration on absolute and relative indices of pulmonary function during eupnoeic respiration and carbon dioxide-induced hyperpnoea (rebreathing) in healthy horses using a pneumotachographic spirometry system. Sedation with acetylpromazine (ACP), xylazine, or both drugs in combination was associated with significant reductions in respiratory frequency, minute ventilation and peak airflows during eupnoeic respiration. Peak expiratory airflow occurred later in the respiratory cycle than was observed in untreated horses, and expiratory relative flow-time indices were also affected during eupnoeic respiration. Rebreathing attenuated the effects of sedation on indices of pulmonary function, suggesting that future studies should consider the use of induced hyperpnoea as part of the spirometry protocol. Based on the finding that all sedative agents had some effect on eupnoeic respiration, albeit least pronounced with ACP, the latter drug should be considered for sedation of horses undergoing PFT. Salbutamol increased peak inspiratory flow during eupnoeic respiration in healthy horses.

Introduction

Pulmonary function testing (PFT) of horses in a clinic or field setting is useful for diagnosis and assessment of respiratory disease, and for monitoring the response to treatment (Hoffman and Mazan, 1999). Studies of relative flow at relative times during breath by breath spirometry have recently been shown to provide reproducible results in healthy horses during tidal breathing (eupnoea) and carbon-dioxide induced hyperpnoea (rebreathing) (Burnheim et al., 2016). It has been hypothesised that relative flow-time indices, or relative airflow at 25%, 50% and 75% of inspiration and expiration times, could provide valid measures of respiratory function in horses. Although in initial studies horses tolerated PFT without sedation, considerable time was invested conditioning the animals to accept the mask and tolerate the rebreathing procedure prior to testing. In a diagnostic setting, many horses may require sedation to ensure tolerance of spirometry procedures, particularly rebreathing.

The administration of sedative agents may confound PFT. The administration of xylazine (XY) has been associated with increased upper airway resistance due to changed pharyngeal patency and nasal mucosal swelling (Lavoie et al., 1992, 1996). Alpha-2 agonists have variable effects on respiratory frequency (Rf), tidal volume (Vt) and minute ventilation in healthy horses and horses with obstructive airway conditions (Lavoie et al., 1996; Herholz et al., 1997), and have also been associated with bronchodilatory effects in horses with recurrent airway obstruction (Broadstone et al., 1992; Lavoie et al., 1996; Hoffman and Mazan, 1998) or in anaesthetised equids (Watney et al., 1988). However, in healthy horses, XY treatment increased airway resistance and reactance during impulse oscillometry testing (Klein et al., 2006). Effects of acetylpromazine (ACP), or ACP and XY combinations, on PFT have been less well characterised. ACP presented bronchodilatory effects in anaesthetised horses (Watney et al., 1988) and, due to reduced abduction of arytenoid cartilages (Lindegaard et al., 2007), may also affect respiratory mechanics via alterations in upper airway resistance.

Salbutamol (SAL), a β_2-adrenergic receptor agonist, induces bronchodilation in horses with acute airway obstruction (Derksen et al., 1999; Bertin et al., 2011), but has no reported effect on breathing mechanics or gas exchange in healthy horses (Bailey et al., 1999; Bayly et al., 2001; Mazan and Hoffman, 2001). Salbutamol was included in the present study due to the exploratory nature of project, and because airway health of study horses could not be ascertained prior to pulmonary function testing.

The current study used breath by breath spirometry to characterise effects of commonly used sedatives and a bronchodilator on absolute and relative indices of pulmonary function during eupnoeic respiration and carbon dioxide (CO_2)-induced hyperpnoea (rebreathing) in healthy horses The research objective was to better characterise the effects of these agents on airflow using a novel approach for analysing respiratory function. It was hypothesised that

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http://dx.doi.org/10.1016/j.tvjl.2017.03.001
1090-0233/

sedation would affect measures of respiratory function and that effects of inhaled salbutamol would be negligible in healthy horses.

Materials and methods

Horses

Eight healthy Standardbred mares (mean ± standard deviation age 6.2 ± 3.3 years and body mass 518 ± 30 kg) were used for this study, which was performed immediately following completion of an initial study to characterise absolute and relative indices of pulmonary function using breath by breath spirometry during eupnoeic respiration and CO_2-induced hyperpnoea (rebreathing) in the same horses without sedation (Burnheim et al., 2016). All horses were housed on site for at least 6 months prior to commencing the study, and none of the horses was routinely engaged in strenuous exercise. No abnormalities were evident in any horse following full clinical examination, haematology and serum biochemistry. Endoscopic assessment of the upper airway demonstrated mildly increased tracheal secretions (grade 2) in four horses, one of which also had increased mast cells (5.7%) in bronchoalveolar lavage fluid (BALF) collected immediately following final spirometry testing. One additional horse had marginally increased eosinophils (2.5%) in BALF. Detailed results of airway cytology for these horses have been published previously (Burnheim et al., 2016).

Horses were accustomed to the stocks, the testing area and to wearing a modified facemask (Aeromask, Trudell Medical International) prior to the start of the study. All pulmonary airflow analyses were performed between 11:00 and 15:00 h and horses were tested in the same order to reduce the effects of circadian rhythm on pulmonary function. An elevated head position was maintained in sedated horses, with head support given if required. Ambient temperature (16.7–20.3 °C) and relative humidity (41–76%) were recorded at the beginning of each test. All horses were housed in a 1-hectare paddock for the duration of the experiment with access to summer grass pasture, and fed lucerne hay once a day. Horses were in a holding yard at for at least 30 min prior to testing to prevent increased respiratory rate due to exercise and excitement. The study design was approved by the Animal Care and Ethics Committee of Charles Sturt University, Wagga Wagga (ACEC approval number 10/077; approval date 9 July 2010).

Spirometry

A modified facemask (Fig. 1) with three bi-directional pitot flow sensors (preVent Flow Sensor, MGC Diagnostics Corporation) was placed over the horse's muzzle covering the nose and mouth, as described previously for breath-by-breath analysis of airflow (Burnheim et al., 2016). Flow sensors were calibrated using a 7 L-certified calibration syringe (Hans Rudolph Incorporated) prior to PFT. During spirometry, gas flow was measured every 10 ms to 0.1 L/s resolution following correction for body temperature and pressure, saturated with water vapour (BTPS) based on daily measurement of barometric pressure, ambient temperature and relative humidity. Each pitot sensor measured airflow to a maximum of 18 L/s, and outputs from each tube were summed and recorded with a CPFS/D Laboratory Spirometer (MGC Diagnostics Corporation). Oxygen and CO_2 concentrations in expired gas were determined (ML206 Gas Analyser, ADInstruments) on a breath to breath basis via a sampling port incorporated into the central flow tube (Fig. 1) and following a two-step calibration procedure utilising room air and Carbogen (5% CO_2, 95% oxygen; BOC Australia). The gas analyser consisted of an infrared CO_2 transducer (range 0–10% CO_2) and a visible spectrum (760 nm) absorption O_2 transducer (range 5–100% O_2) fed from a damped, micro-vacuum pump with a system sampling flow rate of approximately 200 mL/min. Calibration of flow sensors occurred with the gas sampling port in situ, and details of method validation have been published previously (Burnheim et al., 2016). A rubber seal and stoppers were used to ensure the facemask was airtight. Mask fit was assessed visually before and during every recording to ensure it remained airtight.

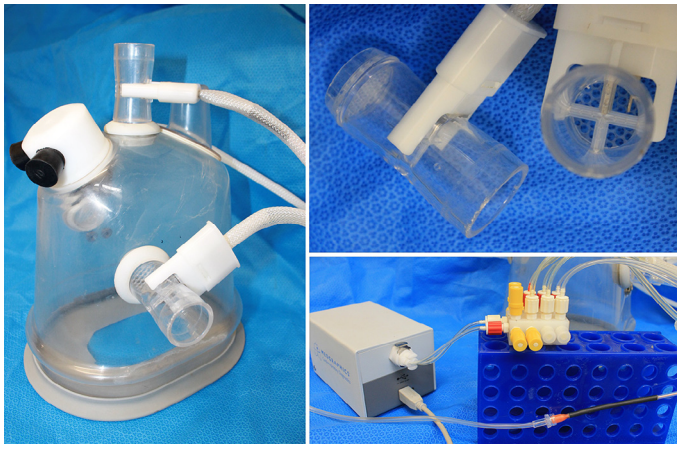

Fig. 1. Spirometry was performed using a facemask modified to accommodate three pitot tubes (left). Each pitot tube (top right) was connected to a manifold (bottom right) to combine flow input from all three tubes. The manifold was connected to a signal transducer. The central pitot tube included a gas sampling port (arrows), connected to a gas analyser (not shown).

Effect of sedation on indices of pulmonary function

On consecutive days, horses were loaded into stocks and fitted with the modified facemask. Once settled, each horse received ACP (0.02 mg/kg; day 1), XY (0.4–0.5 mg/kg; day 2) or ACP (0.02 mg/kg) and XY (0.2 mg/kg) (ACP + XY; day 3) intravenously. Five minutes of eupnoeic breathing was recorded, commencing 20 min, 5 min or 10 min after each respective treatment. These times were selected to coincide with peak activity of each drug or combination of drugs. Airflows during CO_2-induced hyperpnoea were then recorded during and after placement of a plastic bag (capacity 60 L) over the facemask and pitot tubes. One or two attendants, as required, ensured that the bag remained airtight and did not obstruct flow sensors. Recording started once the bag was in place and continued until end-tidal CO_2 levels exceeded 4.5%. The plastic bag was then removed and recording of spirometry measurements was continued until the horse's tidal volume and flow measurements returned to values obtained during eupnoeic respiration.

Effect of inhaled salbutamol on indices of pulmonary function

Based on previous recommendations (Bailey et al., 1999), horses were administered 900 μg SAL (1.2–2 μg/kg, nine actuations at 30 s intervals) by inhalation using an EquineHaler delivery device (Jørgen Kruuse A/S). Each horse then stood quietly in the stocks for 15 min prior to eupnoeic and hyperpnoeic spirometry as described above.

Spirometry measurements

Spirometry recordings from 5 min of eupnoeic breathing and 2–3 min of CO_2-induced hyperpnoeic respiration were evaluated, as previously described (Burnheim et al., 2016). Briefly, from each recording, three representative breaths were selected for analysis. Suitable breathing cycles were free of artefacts such as swallowing or head movement, presented less than 10% difference in inspiratory and expiratory volume, and had comparable flow curves, with peak inspiratory and expiratory flow at similar locations for the three breaths (i.e. all early or late flow peaks). Where possible, three consecutive breaths were selected.

For each selected breath, respiratory frequency (Rf), tidal volume (V_T), total breath period (Tt), inspiratory and expiratory periods (Ti and Te), peak inspiratory and expiratory flows (PIF and PEF), time to PIF (Tpif) and time to PEF (Tpef) were measured; minute ventilation (MVe) and ratios of Te/Tt, Te/Ti, Tpef/Te and Tpif/Ti were calculated. Results for each parameter, thus determined in triplicate, were then averaged to give a final result for each horse during eupnoea and rebreathing. Relative flow-time variables were calculated as previously described (Kusano et al., 2007; Evans et al., 2011; Burnheim et al., 2016). Briefly, the percentage of PEF at 25%, 50% and 75% of the time from initiation of expiration to PEF (Tpef) were identified as ezp25%, ezp50% and ezp75%, respectively. Similar relative flow-time measurements were made for 25%, 50% and 75% of the time from PEF to the end of expiration (epz25%, epz50% and epz75%), and inspiratory phases of each breath were similarly assessed to determine analogous percentages of PIF (izp25%, izp50% and izp75%; ipz25%, ipz50% and ipz75%).

Experimental design and statistical methods

This study was conducted as a prospective observational study, with drugs administered to horses in the following order: Day 1: ACP; Day 2: XY; Day 3: ACP + XY; and Day 4: SAL. All horses received the same order of treatments, and all horses received every treatment. Horses were maintained on pasture for at least 2 months prior to PFT, and for the duration of the study. Baseline PFT data for characterisation of the repeatability of the technique were obtained immediately prior to the current study and have been published separately (Burnheim et al., 2016). The effect of sedation was assessed during eupnoeic breathing and CO_2-induced hyperpnoea by comparison of results for six indices of respiratory function (Rf, Vt, min vent, PEF, PIF, Tpef), two relative flow measures (Tpef/Te and Te/Tt) and 12 relative flow-time values (izp25%, izp50%, izp75%, ipz25%, ipz50%, ipz75%, ezp25%, ezp50%, ezp75%, epz25%, epz50%, epz75%). Untreated results for each horse were derived as the mean value for each parameter, determined over 3 days of repeated testing immediately prior to the current study (Burnheim et al., 2016). Descriptive data are reported as the mean ± standard deviation for each parameter. Within-day coefficients of variation (CV) were calculated for each parameter based on analysis of the three selected breaths.

Results were compared by one-way repeated measures analysis of variance, with separate analyses for eupnoeic and hyperpnoeic ventilation. Data were checked for normality, equal variance and sphericity (equal variability of differences); the Geisser-Greenhouse correction was applied as required. Where a significant treatment or