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Original Article

Cardiopulmonary effects of vatinoxan in sevoflurane-anaesthetised sheep receiving dexmedetomidine

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ABSTRACT

The effects of pre-treatment with vatinoxan (MK-467) on dexmedetomidine-induced cardiopulmonary alterations were investigated in sheep. In a crossover study design with a 20-day washout, seven sheep were anaesthetised with sevoflurane in oxygen and air. The sheep were ventilated with the pressure-limited volume-controlled mode and a positive end-expiratory pressure of 5 cmH_2O. Peak inspiratory pressure (PIP) was set at 25 cmH_2O. The sheep received either 150 μg/kg vatinoxan HCl (VAT + DEX) or saline intravenously (IV) 10 min before IV dexmedetomidine HCl (3 μg/kg, DEX). Cardiopulmonary variables were measured before treatments (baseline), 3 min after vatinoxan or saline, and 5, 15 and 25 min after dexmedetomidine. Computed tomography (CT) of lung parenchyma was performed at baseline, 2 min before dexmedetomidine, and 10, 20 and 30 min after DEX. Bronchoalveolar lavage (BAL) was performed after the last CT scan and shortly before sheep recovered from anaesthesia. After VAT, cardiac output significantly increased from baseline. DEX alone significantly decreased partial arterial oxygen tension, total dynamic compliance and tidal volume, whereas PIP was significantly increased. With VAT + DEX, these changes were minimal. No significant changes were detected in haemodynamics from baseline after DEX. With VAT + DEX, mean arterial pressure and systemic vascular resistance were significantly decreased from baseline, although hypotension was not detected. On CT, lung density was significantly increased with DEX as compared to baseline. No visual abnormalities were detected in bronchoscopy and no differences were detected in the BAL fluid after either treatment. The pre-administration of vatinoxan alleviates dexmedetomidine-induced bronchoconstriction, oedema and hypoxaemia in sevoflurane-anaesthetised sheep.

Introduction

In veterinary clinical practice, α_2-adrenoceptor agonists are used as sedatives, anxiolytics and analgesics, and to reduce general anaesthetic requirements. However, in all species, their use is associated with a number of side effects, most notably bradycardia, vasoconstriction and a reduction in cardiac output. These negative side effects are mainly mediated via peripherally located α_2-adrenoceptors (Bryant et al., 1998).

In small ruminants, particularly sheep, α_2-agonists are known for the induction of arterial hypoxaemia. The intensity of hypoxaemia depends on a number of factors, such as the dose of the agonist, route of administration, age of the animal and inter-individual variation. However, the hypoxaemic effect of α_2-agonists in sheep is primarily mediated via the peripheral α_2-adrenoceptors (Celly et al., 1997). The exact underlying mechanism(s) remain debated among researchers, although several theories have been proposed. Xylazine caused the contraction of isolated sheep tracheal strips (Papazoglou et al., 1995) and increased airway pressure in halothane-anaesthetised sheep (Nolan et al., 1986; Papazoglou et al., 1994). The authors hypothesised that the increased airway pressure was either due to decreased dynamic compliance or increased airway resistance (Nolan et al., 1986; Papazoglou et al., 1994). In addition, pulmonary

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oedema formation as a result of platelet aggregation and pulmonary microembolism (Eisenach, 1988), pulmonary venomotor spasm (Bacon et al., 1998), the release of inflammatory mediators due to the activation of intravascular pulmonary macrophages (Celly et al., 1999a) and increased hydrostatic pressure (Kästner et al., 2007) have also been suggested as the cause of hypoxaemia.

In sevoflurane-anaesthetised sheep, dexmedetomidine induced marked vasoconstriction, with increases in systemic and pulmonary arterial blood pressure, pulmonary occlusion pressure and capillary wedge pressure (Kästner et al., 2005, 2007; Kutter et al., 2006). Furthermore, decreased dynamic compliance, increased airway resistance and an increased pulmonary shunt fraction and dead space ratio were also reported (Kästner et al., 2005, 2007; Kutter et al., 2006).

Vatinoxan (previously named MK-467 and L-659,066) is a peripheral α_2-adrenoceptor antagonist that poorly penetrates the mammalian central nervous system due to its low lipophilicity (Clineschmidt et al., 1988). Vatinoxan has demonstrated an ability to alleviate the adverse cardiopulmonary effects associated with dexmedetomidine in various species, whilst preserving the desired, centrally mediated actions (Raekallio et al., 2010; Honkavaara et al., 2008, 2011, 2017). The aim of the present study was to investigate the ability of vatinoxan to alleviate the adverse cardiopulmonary alterations induced by dexmedetomidine in sevoflurane-anaesthetised sheep. Our hypothesis was that pretreatment with vatinoxan would prevent the increase in airway resistance and pulmonary oedema formation, and consequently reduce the degree of induced hypoxaemia following dexmedetomidine administration.

Materials and methods

Animals

A prospective, randomised, cross-over design was used with a minimum washout period of 20 days between treatments. Seven Texel and Crossbred sheep, 1–3 years of age, with previously exteriorised right carotid arteries and a mean ± standard deviation (SD) body weight of 55 ± 4 kg were used in this study. The animals were deemed healthy based on physical examination, haematology and blood chemistry results. Food was withheld for 24 h prior to each phase of anaesthesia. The study was approved by the national Animal Experiment Board of Finland (license number ESAVI/9394/04.10.07/2015; date of approval 12th January 2016).

Induction and maintenance of anaesthesia

Following the placement of an 18 G cephalic catheter (Terumo), anaesthesia was induced with propofol (Vetofol 10 mg/mL; Norbrook Laboratories) until effect. After endotracheal intubation with a silicone endotracheal tube (9–11 mm internal diameter, MILA International), anaesthesia was maintained at 3.0% end-tidal sevoflurane (SevoFlo; Abbott Laboratories) in 50% oxygen and air (0.5 fraction of inspired oxygen (FiO_2)). The sheep were positioned in sternal recumbency and intermittent positive pressure ventilation (IPPV) was started immediately following intubation with the pressure-regulated volume-controlled (PRVC) mode (Perseus A 500, Dräger); the positive end-expiratory pressure (PEEP) was set at 5 cmH_2O and maintained at a constant level throughout the anaesthesia. Peak inspiratory pressure (PIP) was set initially at 25 cmH_2O and, if required due to a decrease in pulmonary compliance, increased to 30 cmH_2O to achieve a tidal volume (V_T) of 12 mL/kg and an end-tidal carbon dioxide concentration ($ETCO_2$) of 40 mmHg. At the beginning of anaesthesia, an inspiratory-expiratory ratio (I:E) of 1:2 and respiratory rate (f_R) of 11–13 breaths per min were set, but they were adapted as necessary during the anaesthetic to maintain normocapnia. Parameters monitored and recorded every 5 min were rectal temperature, haemoglobin oxygen saturation (SpO_2), pulse rate (Nonin PalmSAT 2500 series), f_R, FiO_2, $ETCO_2$, end-tidal sevoflurane, V_T, minute volume (M_V), total dynamic compliance (C_{dyn} mL/cmH_2O) and PIP. Airway gas concentrations were measured from the proximal end of the endotracheal tube.

Instrumentation

The animals were instrumented with a right carotid arterial catheter (20 G; B. Braun Melsungen AG), a right jugular catheter (16 G; MILA International) and a pulmonary artery catheter (7 Fr, 110 cm, triple-lumen Swan-Ganz monitoring catheter; Edwards Lifesciences) via the left jugular vein. The correct placement of the pulmonary artery catheter was confirmed by the shape of pressure waves and subsequently confirmed with CT. All catheters were secured in position with skin sutures. Following instrumentation, a stomach tube was passed into the rumen. Invasive arterial blood pressure (IBP), central venous pressure (CVP) and pulmonary arterial pressure (PAP) were measured (Datex Engstrom S/5 monitor, Datex Ohmeda) using pre-calibrated pressure transducers (Gabarith PMSET; Becton Dickinson). The height at the shoulder joint was used as the zero reference point for all blood pressure measurements. Cardiac output (CO) was measured using the lithium dilution method (LiDCO plus Haemodynamic Monitor; LiDCO). Anaerobic blood samples were obtained in pre-heparinised syringes (Pico50; Radiometer) for arterial and mixed venous blood gas analysis and were placed in iced water for immediate analysis (ABL 855; Radiometer). The blood gases were corrected for rectal temperature. Blood samples for the determination of plasma dexmedetomidine and vatinoxan concentrations were collected from the carotid artery catheter, centrifuged at 3000 *g* for 15 min, and frozen at −20 °C until analysed.

Study protocol

Immediately after instrumentation, the animals were moved to the CT suite. After baseline cardiopulmonary measurements and a baseline thoracic CT scan, an intravenous (IV) bolus of either 150 μg/kg vatinoxan hydrochloride (vatinoxan HCl; Vetcare), diluted in saline to achieve a concentration of 0.5%, or a similar volume of saline was injected (T-10; VAT + DEX; DEX). All cardiopulmonary measurements were repeated 3 min later (T-7), followed by a CT scan (T-2). After the second CT scan, 3 μg/kg dexmedetomidine HCl (Dexdomitor 0.1 mg/mL, Orion Pharma) diluted in 20 mL saline was injected IV over 30 s 10 min after vatinoxan or saline (T0), and all cardiopulmonary measurements were repeated 5, 15 and 25 min after dexmedetomidine (T5, T15 and T25). The CT scan was repeated at 10, 20 and 30 min (T10, T20 and T30) after dexmedetomidine administration (Fig. 1).

The CT scan of the lungs (GE Lightspeed VCT 64, GE Healthcare) was performed at 140 kV, mA noise index 18.0 (min 120 mA/max 710 mA), slice thickness 0.625 mm, time/rotation 0.4 sec and pitch 0.984. A lung algorithm was used and all images were evaluated with a window level of −500 and window width of 1500. The CT scanner was calibrated daily according to the hospital's procedure. The cross-sectional areas of the right caudal pulmonary artery and vein were measured at the level of the proximal dorsocaudal branch of the vein according to Kästner et al. (2007). Two regions of interest (ROI) of 0.5 cm^2 were drawn on this same image: one positioned dorsally (ROI 1), close to the periphery of the lung parenchyma, and the other ventrolateral (ROI 2) to the main bronchus as shown in Fig. 3A, and the CT values of each ROI were calculated as Hounsfield units (HU). The measurements were conducted three times with an interval of at least 1 week by an investigator blinded to the treatments and time points, and the mean values were used.

Bronchoscopy and bronchoalveolar lavage (BAL) were performed via the endotracheal tube approximately 5 min after the last CT scan. Fifty millilitres of saline was infused through the work channel of the bronchoscope (Olympus

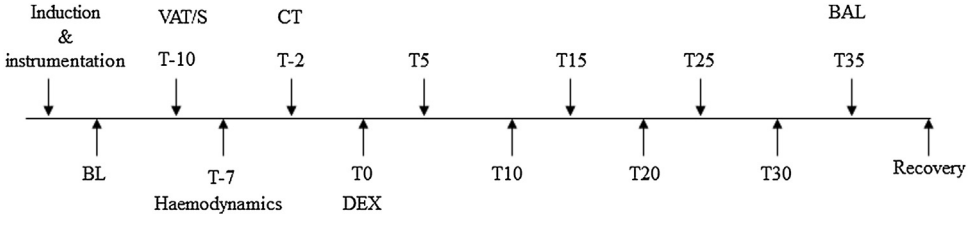

Fig. 1. Experimental timeline. BAL, bronchoalveolar lavage; BL, baseline measurements; CT, computed tomography; DEX, dexmedetomidine; S, saline; T-10, 10 min before dexmedetomidine administration; VAT, vatinoxan.