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RESEARCH PAPER

Sedative and cardiopulmonary effects of xylazine alone or in combination with methadone, morphine or tramadol in sheep

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Abstract

Objective To evaluate the cardiopulmonary and sedative effects of xylazine alone or in combination with methadone, morphine or tramadol in sheep.

Study design Experimental, prospective, crossover, randomized, blinded study.

Animals Six Santa Inês breed sheep (females) aged 12 ± 8 months and weighing 39.5 ± 7.4 kg.

Methods Sheep were sedated with each of four treatments in a randomized, crossover design, with a minimum washout period of 7 days between treatments. Treatments were: X [xylazine (0.1 mg kg^{-1})]; XM [xylazine (0.1 mg kg^{-1}) and methadone (0.5 mg kg^{-1})]; XMO [xylazine (0.1 mg kg^{-1}) and morphine (0.5 mg kg^{-1})], and XT [xylazine (0.1 mg kg^{-1}) and tramadol (5 mg kg^{-1})]. Each drug combination was mixed in the syringe and injected intravenously. Sedation, heart rate (HR), mean arterial blood pressure (MAP), rectal temperature (RT°C), respiratory rate (f_R), arterial blood gases and electrolytes were measured before drug administration (T0) and then at 15 minute intervals for 120 minutes (T15–T120).

Results Heart rate significantly decreased in all treatments compared with T0. $PaCO_2$ values in XM and XMO were higher at all time points compared with T0. In treatments X and XM, pH, bicarbonate (HCO_3^-) and base excess were increased at all time points compared with T0. PaO_2 was significantly decreased at T15–T75 in XM, at all time points in XMO, and at T15 and T30 in XT. Sedation at T15 and T30 in XM and XMO was greater than in the other treatments.

Conclusions and clinical relevance The combinations of methadone, morphine or tramadol with xylazine resulted in cardiopulmonary changes similar to those induced by xylazine alone in sheep. The combinations provided better sedation, principally at 15 minutes and 30 minutes following administration.

Keywords α_2-agonists, opioids, ovine, sedation.

Introduction

Xylazine is 10–20 times more potent in ruminants than in other species (Kästner 2006). Cardiopulmonary effects include bradycardia, changes in arterial blood pressure, tachypnea accompanied by

pulmonary edema and arterial hypoxemia (Bacon et al. 1998; Kästner 2006). Death resulting from the development of pulmonary edema after administration of xylazine has also been reported (Uggla & Lindqvist 1983). Despite these profound cardiopulmonary effects, sedation may not be as pronounced as expected, and recumbency may not be induced when xylazine is administered to sheep intravenously (IV) or intramuscularly (IM) (Kästner 2006). Therefore, combining xylazine with other drugs may be useful to enhance sedation.

Morphine and methadone are classified as full μ-agonists and are widely used in veterinary practice, alone or in combination with other drugs for premedication and analgesia. However, the reported use of these drugs in ruminants is rare. Studies on drug residues are lacking, which may limit the clinical usefulness of opioids in food animal practice (KuKanich & Papich 2009). Tramadol may be classified as an atypical opioid drug because much of its analgesic action is attributable to a central effect in inhibiting the reuptake of serotonin and noradrenaline, and it also shows relatively weak action at opioid μ-receptors (KuKanich & Papich 2009). Adverse effects following its administration include sedation, although there are few data on its administration as part of a premedication or sedation protocol in sheep. Guedes et al. (2005) demonstrated that tramadol alone administered IM to dogs prior to general anesthesia did not produce any visible sedation. Excitatory effects on the central nervous system (CNS), such as agitation and nystagmus, following the administration of opioids to ruminants have been described (Waterman et al. 1990, 1991; Lin & Riddell 2003; Edmondson et al. 2012), and may counteract the level of sedation observed.

Combinations of sedatives and opioid drugs are commonly used in veterinary anesthesia because they have useful synergistic effects. This synergism enhances sedation and analgesia and may facilitate a significant reduction in the doses of both drugs, thereby reducing the adverse cardiopulmonary effects associated with each drug when it is administered alone. Numerous studies in dogs and cats have demonstrated that sedation is better when an α_2-agonist is administered in combination with an opioid than when the α_2-agonist is administered alone (Selmi et al. 2003; Leppänen et al. 2006; Monteiro et al. 2008; Cardoso et al. 2014).

The aim of this study was to examine the cardiopulmonary and sedative effects of xylazine in combination with different opioids when administered IV in sheep. The study hypothesis was that sedation would be superior following the administration of these combinations compared with the administration of xylazine alone.

Materials and methods

This research was conducted with the approval and supervision of the Ethics Committee on Animal Use of the University of Franca, Brazil (protocol no. 038/12). All procedures were conducted in compliance with the ethical principles of good practice in animal experimentation.

Animals

Six female, non-pregnant Santa Inês sheep, with a mean ± standard deviation (SD) age of 12 ± 8 months and mean ± SD weight of 39.5 ± 7.4 kg were used. The animals were kept collectively in 6 × 6 m plots and were given hay, pelleted feed and mineral supplements on a daily basis, and water *ad libitum*. Prior to the study, the health of the animals was evaluated using a complete blood count, liver and renal biochemical profile, and fecal parasitologic examination. For at least 20 days prior to the initiation of the study, the animals were monitored for individual behavior and were conditioned to physical restraint. Before the study, food and water were withheld for 24 hours and the hair over the right jugular vein and auricular arteries was clipped.

Once the animals were moved to the experimental area, the skin sites for vessel catheterization were aseptically prepared. A catheter (18 gauge, 2.5 cm Safelet; Nipro Medical Ltda, SP, Brazil) was introduced into the right jugular vein, and a second catheter (20 gauge, 2.5 cm) introduced into an auricular artery with the sheep restrained in a standing position. The ambient temperature was 22 °C. Fifteen minutes were allowed to elapse following instrumentation before any measurements were recorded.

Experimental design

The sheep were randomized (by drawing of lots) to four treatments in a crossover study, with a minimum interval of 7 days between treatments. The four treatments were: X, xylazine (0.1 mg kg^{-1}; Rompun 2%; Bayer AG, SP, Brazil); XM, xylazine

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