Behavioral and cardiopulmonary effects of dexmedetomidine alone and in combination with butorphanol, methadone, morphine or tramadol in conscious sheep

Abstract

Objective To compare cardiopulmonary and sedative effects, blood gas values and temperatures following administration of dexmedetomidine alone or with butorphanol, methadone, morphine or tramadol in healthy sheep.

Study design Randomized crossover study.

Animals Six Santa Inês sheep, five females, one male, aged 12-28 months and weighing 40.1 ± 6.2 kg.

Methods Sheep were assigned treatments of dexmedetomidine (0.005 mg kg^{-1}; D); D and butorphanol (0.15 mg kg^{-1}; DB); D and methadone (0.5 mg kg^{-1}; DM); D and morphine (0.5 mg kg^{-1}; DMO); D and tramadol (5.0 mg kg^{-1}; DT). All drugs were administered intravenously with at least 7 days between each treatment. Rectal temperature, heart rate (HR), respiratory rate (f_R), invasive arterial pressures, blood gases and electrolytes were measured prior to administration of drugs (baseline or T0) and every 15 minutes following drug administration for 120 minutes. Sedation was scored by 3 observers blinded to treatment.

Results HR decreased in all treatments and f_R decreased in DM at T30 and DMO at T30 and T45. $PaCO_2$ was increased in D, DB and DM compared with baseline, and PaO_2 decreased in D at T15 and T45; in DB at T15 to T75; in DM at T15 to T60; in DMO at T15; and in DT at T15, T30 and T75. Decreased temperature occurred in D, DB and DM. An increased pH was

measured in D at all time points and in DT at T30 to T120. HCO_3^- and base excess were increased in all treatments compared with baseline. There were no statistical differences in sedation scores.

Conclusions and clinical relevance The combination of dexmedetomidine with butorphanol, methadone, morphine or tramadol promotes similar changes in cardiopulmonary function compared with dexmedetomidine alone. Sedation was not improved using these combinations when compared with the administration of dexmedetomidine alone.

Keywords α_2-agonists, cardiorespiratory, opioids, ovine.

Introduction

Alpha$_2$-adrenergic agonists (α_2-agonists) are used for sedation and premedication prior to general anesthesia in several species. Racemic medetomidine has a binding ratio of 1620: 1 (α_2:α_1) (Virtanen et al. 1988) and its d-enantiomer – dexmedetomidine – is even more selective (Murrell & Hellebrekers 2005). Advantages of α_2-agonists include potent, predictable sedation (Cardoso et al. 2014), analgesia, reduced anesthetic requirement, and reversibility (Murrell & Hellebrekers 2005).

In sheep, α_2-agonists are widely used for provision of analgesia and sedation (Kästner 2006). However, arterial hypoxemia and pulmonary edema have been reported in certain breeds of sheep following the administration of all α_2-agonists including dexmedetomidine (Celly et al. 1997; Kästner et al. 2001b; Kästner 2006). Congestion and redistribution of blood flow have been suggested as the cause of impaired oxygenation following the administration of dexmedetomidine to healthy anesthetised sheep. The hypoxemia is made worse by alveolar edema as a result of hydrostatic stress (Kästner et al. 2007). Dexmedetomidine has been compared to medetomidine in sheep, and has similar cardiopulmonary and sedatives effects (Kastner et al. 2001a), but combinations of dexmedetomidine and opioids have not yet been described.

The administration of dexmedetomidine with opioids to dogs (Cardoso et al. 2014), and xylazine with opioids to sheep (Carvalho et al. 2015), improves sedation when compared with administraion of the α_2-agonist alone. Combining dexmedetomidine with opioids in conscious sheep may facilitate certain procedures, and lower doses might reduce the incidence and severity of side effects.

The aim of this study was to compare the cardiopulmonary and sedative effects of dexmedetomidine alone or in combination with butorphanol, methadone, morphine or tramadol in sheep. Our hypothesis was that these combinations may improve sedation without

inducing significant cardiopulmonary depression when compared with administration of dexmedetomidine alone.

Materials and methods

This research was conducted following approval from The Animal Ethics Committee of University of Franca, protocol no. 038/12. The research facility is located 1040 metres above sea level. The reader is directed to a previous associated study for detailed information regarding the management and assessment of animals prior to experimentation, and also for further details of measurement methods (Carvalho et al. 2015).

Animals

Six Santa Inês sheep, five females and one male, aged 12 - 28 months and weighing 40.1 ± 6.2 kg were used. Catheters were inserted aseptically into a jugular vein (18 gauge, 2.5 cm) and an auricular artery (20 gauge, 2.5 cm) with the sheep standing. Variables were measured prior to the administration of drugs (baseline, T0) and then every 15 minutes following the administration of drugs for 120 minutes (T15 – T120).

Experimental design

Sheep were administered treatments in random order (by drawing lots) in a crossover design with a washout period of 7 days between treatments. The treatments were: D (dexmedetomidine 0.005 mg kg^{-1}; Dexdomitor 0.5 mg mL^{-1}, Pfizer, UK); DB (dexmedetomidine 0.005 mg kg^{-1} and butorphanol 0.1 mg kg^{-1}; Torbugesic, 10 mg mL^{-1}; Forte Dodge, Iowa, USA); DM (dexmedetomidine 0.005 mg kg^{-1} and 0.5 mg kg^{-1} methadone; Mytadon, 10 mg mL^{-1}; Cristália Produtos Químicos e Farmacêuticos Ltda, SP, Brazil); DMO (dexmedetomidine 0.005 mg kg^{-1} and 0.5 mg kg^{-1} morphine; Dimorf, 10 mg mL^{-1}; Cristália

Produtos Químicos e Farmacêuticos Ltda, SP, Brazil) or DT (dexmedetomidine 0.005 mg kg^{-1} and 5.0 mg kg^{-1} tramadol; Tramadon; 50 mg mL^{-1}; Cristália Produtos Químicos e Farmacêuticos Ltda, SP, Brazil). After instrumentation, a 15-minute period of stabilization prior to data collection elapsed. All drugs administered were mixed in the same syringe with the final volume adjusted to 10 mL with 0.9% sodium chloride to facilitate blinding and given intravenously (IV) over 30 seconds into the jugular catheter.

Degree of sedation

The degree of sedation was assessed using a numerical rating scale of 0-10: 0, no sedation; 1, standing, alert, reduced head and ear movements; 2, standing, slight head drop; 3, standing, moderate head drop; 4, standing, severe head drop, ataxia; 5, standing, severe head drop, severe ataxia; 6, sternal recumbency, head up; 7, sternal recumbency, head down; 8, lateral recumbency, occasional attempts to attain sternal recumbency; 9, lateral recumbency, uncoordinated movements; and 10, lateral recumbency, no movements (Kästner et al. 2003; Carvalho et al. 2015).

Cardiopulmonary variables and rectal temperature

Heart rate (HR) was counted by thoracic auscultation with a stethoscope and respiratory rate (f_R) by observation of thoracic excursions, each over one minute. Mean arterial pressure (MAP) was measured from an auricular artery catheter connected to an aneroid manometer (Indústria Bic de Aperelhos Médicos Ltda, SP, Brazil) by tubing filled with 0.1% heparin solution (50 IU mL^{-1}) and the air-saline junction aligned with the point of the shoulder in standing and sternally recumbent animals and the xiphoid process in laterally recumbent animals (Carvalho et al. 2015), hypotension was defined with values < 60 mmHg. Rectal

temperature (RT°C) was measured with a mercury-in-glass thermometer (Thermometer BD; Becton Dickinson Indústrias Cirurgicas SA, MG, Brazil).

Blood gases and electrolytes

Arterial blood samples were collected for determination of pH, partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), base excess (BE), arterial hemoglobin oxygen saturation (SaO_2), bicarbonate (HCO_3^-), sodium (Na^+), potassium (K^+) and chloride (Cl^-) concentrations. Each sample was 0.5 mL withdrawn from the arterial catheter into a disposable heparinized syringe and sealed with a rubber stopper. Blood samples were analysed immediately [Cobas b 121; Roche Diagnostics (Schweiz) AG, Switzerland]. Hypoxemia was defined with values of $PaO_2 < 60$ mmHg.

Statistical analysis

The results were analyzed using a statistical analysis software program GraphPad PRISM Version 5.0 (GraphPad Software, Inc., CA, USA). Normality was assessed using the Shapiro-Wilk test. Normally distributed data were analysed using analysis of variance (ANOVA) for repeated measures. *Post hoc* analysis within the same treatment group was performed using Dunnett's test and between treatment groups using Bonferroni correction. Non-parametric data were analysed using the Friedman test followed by *post hoc* Dunn's test. For all data $p < 0.05$ were considered to be significant.

Results

All animals completed the 120 minutes of evaluation. Behavioral effects other than sedation included salivation, mydriasis, bruxism (teeth grinding), vocalization and facial muscle tremors (Table 1). The sheep recovered from sedation without further complications.

139

140 Sedative effects

141 Sedation scores were significantly higher compared with baseline at T15 to T60 in D and DT;
142 at T15 to T75 in DB and DM; at T15 to T90 in DMO (Fig. 1). There was no significant
143 difference in the comparative analysis between treatments. Sternal or lateral recumbency
144 (scores 6-10) occurred in D at 4 time points (T45-T90); DB and DM at 4 time points (T15 to
145 T60); DMO at five time points (T15 to T75). Recumbency did not occur in any animal in DT
146 (Fig. 1).

147

148 Cardiopulmonary variables and rectal temperature

149 There was a significant reduction in HR at all time points compared with baseline in D, DB
150 and DT; in DM at T45, T75 and T105; DMO at T15 to T60. There were no significant
151 differences among treatments (Table 2). With the exception of T105 in DT, MAP did not
152 change significantly from baseline in any treatment, and there were no significant differences
153 among the treatments.

154 Temperature decreased significantly from baseline in D at T60 and T75, in DB at T45
155 to T120, and in DM at T45, T75 and T90. There were no significant differences in RT among
156 the treatments.

157 Significant decreases were measured in f_R compared with baseline in DM at T30 and
158 in DMO at T30 to T60. There were no significant differences among treatments.

159

160 Blood gas and electrolyte analysis

161 Mean pH values were higher compared with baseline in D at all time points, in DB at T90 to
162 T120, in DT at T60 to T120 (Table 3). There was no significant difference in pH among

163 treatments. There was a significant increase in $PaCO_2$ compared with baseline at all time
164 points in D and DB; in DM at T15 to T90, with no difference among treatments.

165 There was a significant increase in $[HCO_3^-]$ compared to baseline in group D, DB and
166 DM at T15 to T120; in group DMO at T15 to T105; in group DT at T30 to T120 minutes.
167 Base excess was significantly increased compared to baseline in group D at T45 to T120
168 minutes; in group DB all time points; in group DM at T30 to T90; in group DMO at T45 and
169 T60; in group DT at T30 to T120. There was no significant difference between groups in BE
170 and $[HCO_3^-]$.

171 There was a significant decrease in PaO_2 compared to baseline in group D at T15 and
172 T45; in group DB at T15 to T75; in group DM at T15 to T60; in group DMO at T15; in group
173 DT at T15, T30 and T75. There were no significant differences between groups. Arterial
174 oxygen saturation was significantly lower at T15 compared to baseline in D, DB, DM and
175 DMO; in DT at time points T15 and T30. SaO_2 was significantly lower in group DM at T15
176 compared to other treatments.

177 Sodium concentration was significantly increased compared to baseline in group
178 DMO at T105; in group DT at T90 to T120. There was no significant difference between
179 groups. Potassium was significantly reduced compared to baseline in group DMO and DT at
180 T90 to T120; $[K^+]$ was significantly higher in group DB compared to other groups at T120
181 minutes. Chloride was significantly lower compared to baseline in group DB at T15 and T30.
182 There was no significant difference between groups (electrolyte data not reported)

183

184 **Discussion**

185 Dexmedetomidine has been used in sheep as premedication prior to general anesthesia
186 (Kastner et al. 2001a, 2001b, 2007; Kästner 2006; Granados et al. 2012; Funes et al. 2014).
187 Doses administered ranged from 0.0025 mg kg^{-1} to 0.015 mg kg^{-1} in these studies. Concurrent

188 administration of dexmedetomidine and an opioid results in significantly enhanced sedation
189 without additional cardiopulmonary side effects (Cardoso et al. 2014). A relatively low dose
190 of dexmedetomidine (0.005 mg kg^{-1}) was chosen for this study as it was to be combined with
191 a variety of opioids. It is possible that our dose of dexmedetomidine in this present study was
192 not equipotent to the dose of xylazine administered in a previous associated experiment
193 (Carvalho et al. 2015). This may explain the differing sedative effects. This is reflected in the
194 fact that sedation scores were higher and recumbency was induced in sheep receiving
195 dexmedetomidine alone in this present study, whilst sheep receiving xylazine alone in our
196 previous study (Carvalho et al. 2015), did not become recumbent and median scores were
197 lower.

198 Equipotent doses of opioids are not reported in sheep and, therefore, the dose rates
199 chosen for this study were based on studies performed in dogs (Mastrocinque & Fantoni
200 2003; Maiante et al. 2009) and were identical to those used in a previous associated study in
201 sheep (Carvalho et al. 2015). Superior sedation was expected in sheep administered
202 dexmedetomidine with an opioid compared with dexmedetomidine alone. However,
203 methadone, morphine and butorphanol did not increase the sedation score although sedation
204 was prolonged. In contrast, tramadol administered in combination with dexmedetomidine did
205 not increase the sedation score or prolong the sedation. This is in contrast to our previous
206 study in which sedation was enhanced when an opioid was combined with xylazine (Carvalho
207 et al. 2015). An explanation may be that dexmedetomidine appeared to provide greater
208 sedation when administered alone and therefore an additional sedative effect of the opioid
209 might not have been as obvious.

210 The duration for collection of data was based on the reported duration of sedative
211 effects of morphine, methadone and tramadol in combination with dexmedetomidine in dogs

212 (Cardoso et al. 2014), and that most clinical procedures undertaken in sedated sheep will not
213 exceed 2 hours.

214 The central nervous system (CNS) excitatory effects of opioids administered alone or
215 in combination with α_2-agonists in ruminants have been described (Waterman et al. 1990,
216 1991; Levine et al. 1992; Lin & Riddell 2003; Edmondson et al. 2012; Verbeek et al. 2012;
217 Carvalho et al. 2015). Lin & Riddell (2003) reported the administration of butorphanol alone
218 to cattle induced agitation, vocalization, distress and violent kicking for 2 to 3 minutes after
219 injection. However, administering detomidine in combination with butorphanol appeared to
220 suppress this excitatory effect. The administration of tramadol IV to alpacas resulted in severe
221 CNS excitation: hyperesthesia, tremors, and ataxia (Edmondson et al. 2012). The behavior of
222 sheep after IV morphine includes an increase of locomotor activity, vocalization and escape
223 behavior (Verbeek et al. 2012). Signs of CNS excitation were observed in the sheep in the
224 study presented here following the administration of opioids, similar to those reported in an
225 associated study in sheep where xylazine was combined with opioids (Carvalho et al. 2015).
226 The excitation may have influenced the degree of sedation. Furthermore, opioid-induced
227 behavioral changes, such as bruxism, may mimic pain-related behavior.

228 Heart rate in all treatments was significantly reduced at almost all time points when
229 compared with baseline. This was expected due to the cardiovascular effects of α_2-agonists
230 and in agreement with findings in other species (Murrell & Hellebrekers 2005; Cardoso et al.
231 2014). Initially hypertension occurs due to peripheral vasoconstriction, followed by an
232 increase in vagal tone and a fall in HR. Blockade of sympathetic outflow from the CNS leads
233 to a longer period of bradycardia (Murrell & Hellebrekers 2005). Opioids may potentiate a
234 reduction in HR by vagomimetic effects (Benyamin et al. 2008). However, in conscious goats,
235 methadone administration alone (0.2 mg kg^{-1} IV or 0.6 mg kg^{-1} subcutaneously) did not
236 reduce HR (Olsén et al. 2013). Similarly, butorphanol (0.5 mg kg^{-1} IV) administered alone to

conscious sheep did not affect HR (O'Hair et al. 1988). In this present study, when opioids were combined with dexmedetomidine there was no significant difference among treatments and the majority of the fall in HR can be attributed to dexmedetomidine alone. Hypotension following the administration of xylazine to sheep has been reported (Aziz & Carlyle 1978), but others have not demonstrated this (Grant & Upton 2001; Carvalho et al. 2015). Medetomidine administered IV to sheep did reduce blood pressure during the second (central) phase, but the reduction in MAP did not appear to be clinically significant (Bryant et al. 1998). Dexmedetomidine administered IM (Kastner et al. 2001a) to conscious sheep did not significantly affect blood pressure. Hypotension was not evident in sheep in the present study. The changes in HR and MAP reported here are similar to the changes observed after administration of xylazine and different opioids (Carvalho et al. 2015)

The respiratory depressant effects of dexmedetomidine have been reported in humans (Belleville et al. 1992) and horses (Bettschart-Wolfensberger et al. 2005), although this is not always accompanied by hypercapnia. In humans, opioids exhibit a dose-dependent effect on the respiratory system (Gutstein & Akil 2006), but in animals this is less apparent (Dugdale 2010). Depression occurs in a dose-dependent manner, with a decrease in rate but overall minute volume may not change due to compensatory increases in tidal volume (Dugdale 2010). Evidence in ruminants is relatively sparse. Waterman et al. (1991) reported that butorphanol administered to healthy sheep did not affect respiratory blood gas tensions. More potent opioids such as fentanyl can induce short periods of respiratory depression (Waterman et al. 1990).

Methadone administered IV to pygmy goats induced evidence of hyperventilation (Neal & Olsen 1980). Kastner et al. (2001a) did not demonstrate significant changes in f_R following intramuscular administration of dexmedetomidine to sheep. In this present study, $PaCO_2$ increased in sheep administered dexmedetomidine alone or in combination with

butorphanol or methadone at all time points compared to baseline, indicating some degree of hypoventilation, although alterations were relatively minor and were not deemed clinically significant. This is similar to our findings in a previous study in which sheep administered xylazine, in combination with methadone or morphine, had significant (but minor) elevations in $PaCO_2$ (Carvalho et al. 2015).

Hypoxemia is often observed in sheep following the administration of low doses of dexmedetomidine (Kästner et al. 2007), and there may be significant variation between individual sheep (Kästner 2006). Several mechanisms have been proposed for α_2-agonist induced hypoxemia in sheep: intense venous spasm mediated via adrenoreceptor agonism, pulmonary congestion, increased microvascular pressure and alveolar capillary rupture, resulting in an inflammatory response (Bacon et al. 1998; Kästner et al. 2007). In this present study, there were significant reductions in PaO_2, but the magnitude of the changes differed between animals. Recumbency following drug administration occured in all treatments except DT and therefore a positional influence on gas exchange may have occurred. Lateral recumbency induces a fall in arterial oxygenation when compared to standing sheep (Mitchell & Williams 1977). In the present study, clinically relevant reductions in PaO_2 values were observed in individual animals, therefore oxygen supplementation might be required in some sheep.

In this study, pH, $[HCO_3^-]$ and BE tended to increase over time. Significant increases in pH mainly occurred in sheep treated with dexmedetomidine alone. This may be because some sheep had relatively high pH values at baseline and therefore further increases were not statistically significant. Epidural xylazine in sheep has been associated with increases in pH and bicarbonate, indicative of a metabolic alkalosis; the authors did not speculate as to why this may have occurred (Aminkov & Hubenov 1995). Ringer et al. (2013) identified increases in pH, bicarbonate and BE in horses receiving a 3 hour infusion of xylazine or romifidine due

to a urinary loss of chloride. In our study there were no significant chloride changes and we cannot corroborate this hypothesis in sheep and the cause remains uncertain. Increased pH may explain the rise in $PaCO_2$ observed in some sheep in this study – if hydrogen ion content falls, compensation occurs by hypoventilation and an increase in carbon dioxide attenuating the alkalosis. However, it is likely that sheep had a mixed acid base disturbance with concurrent metabolic alkalosis and respiratory acidosis.

In conclusion, the degree of sedation resulting from combinations of IV dexmedetomidine (0.005 mg kg^{-1}) and either butorphanol, methadone, morphine or tramadol was similar to that from the administration of dexmedetomidine alone. Changes in cardiopulmonary variables were not clinically significant. However, oxygenation should be monitored, and oxygen supplementation provided if necessary. As the number of animals and drugs doses used in this study were limited, further investigations of different dose rates may identify a more effective combination for clinical use.

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