The comparative hypoxaemic effect of four α_2 adrenoceptor agonists (xylazine, romifidine, detomidine and medetomidine) in sheep

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In the present study, the hypoxaemic potential of four α_2 agonists possessing different selectivity for α_2 adrenoceptors and of a saline placebo was studied in five clinically healthy sheep using a randomized Latin square design and equipotent sedative doses. Baseline values for heart rate (HR), mean arterial pressure (MAP), arterial oxygen (PaO_2) and carbon dioxide ($PaCO_2$) tensions, respiration rate and maximum change in pleural pressure (ΔPpl) were obtained, followed by the intravenous administration of either: xylazine (150 μg/kg); romifidine (50 μg/kg); detomidine (30 μg/kg); medetomidine (10 μg/kg) or placebo. Subsequent recordings were made up to 60 min after drug administration. No significant ($P \leqslant 0.05$) alterations in any variable occurred with placebo. All the α_2 agonists significantly ($P \leqslant 0.05$) decreased PaO_2 levels without a significant ($P \leqslant 0.05$) change in $PaCO_2$. The lowest PaO_2 values were 29–42 mm Hg (3.9–5.5 kPa) with no significant difference between drugs. Respiratory rate and ΔPpl increased significantly within 2 min of drug administration; the duration of this effect varied with the α_2 agonist, lasting longest with romifidine. As compared to the saline treated group, a significant increase in MAP was observed up to 10 min after administration of romifidine and detomidine, however, a significant decrease was seen at 10 and 45 min after xylazine and medetomidine, respectively. The α_2 agonists studied induced a similar change in PaO_2 at peak effect, despite their reported variable selectivity for α_2 vs. α_1 adrenoceptors.

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INTRODUCTION

Alpha$_2$ adrenoceptor agonists (α_2 agonists), such as xylazine, are commonly used sedative analgesics in veterinary medicine. A recent report states that each year about seven million veterinary patients receive an α_2 agonist either as a sedative analgesic or as an anaesthetic adjunctive agent (Maze & Tranquilli, 1991). Though α_2 agonists such as xylazine do not cause hypoxaemia at clinical sedative doses in dogs (Haskin *et al.*, 1986), severe hypoxaemia is seen following intravenous (i.v.) administration of xylazine at both sedative and non-sedative doses in sheep (Doherty *et al.*, 1986; Nolan *et al.*, 1986). In cattle, hypoxaemia following intramuscular administration of xylazine was reported as early as 1971 (DeMoor & Desmet, 1971). Later, it was reported in sheep following administration of xylazine (Mitchell & Williams, 1977; Aziz & Carlyl, 1978; Raptopoulos *et al.*, 1985; Doherty *et al.*, 1986; Nolan *et al.*, 1986; Waterman *et al.*, 1987; Hsu *et al.*, 1989) and clonidine (Eisenach, 1988).

The exact mechanisms by which α_2 agonists bring about hypoxaemia are not clear, but various studies have been conducted in an attempt to unravel them. Nolan *et al.* (1986) and Eisenach (1988) studied the effect of xylazine and clonidine on various cardiopulmonary variables in an attempt to identify the origin of hypoxaemia. Another approach has been the use of inhibitory agents other than specific α_2 adrenoceptor antagonists to identify causative mechanisms (Nolan *et al.*, 1990). Pretreatment with aspirin has been used to test for the involvement of the cyclo-oxygenase system (Nolan *et al.*, 1990). Similarly, the role of histamine has been tested by pretreatment with antihistaminic agents (Nolan *et al.*, 1986). Neither of these were found to play a role in xylazine-induced hypoxaemia.

Xylazine was the first α_2 agonist used as a sedative analgesic in veterinary practice (Clarke & Hall, 1969). In the 1980s, two new α_2 agonists, detomidine (Clarke & Taylor, 1986) and medetomidine (Savola *et al.*, 1986), were introduced as sedative analgesic agents for large and small animals, respectively. These compounds are more specific α_2 agonists than xylazine. On a comparative basis, medetomidine is about 10, 7 and 6 times more selective for α_2 adrenoceptors than are xylazine, clonidine and detomidine, respectively (Virtanen *et al.*, 1988).

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One of the major advantages of developing drugs with high receptor specificity and affinity is the low dose required to achieve desirable effects and freedom from unrelated side effects. For instance, in cattle, the sedative dose of xylazine is 200 μg/kg i.v. (Doherty *et al.*, 1987), whereas the comparable dose of detomidine is 10 μg/kg (Peshin *et al.*, 1993). It is not known, however, whether increasing specificity for the α_2 adrenoceptors affects the comparative hypoxaemic potential of these compounds. Moreover, interpretation of most of the studies where α_2 agonist-induced hypoxaemia was examined is clouded by the fact that the animals also changed their body position during the onset of sedation, or they were in a body position that lowers arterial oxygen tension (PaO_2) because of changes in lung volume and ventilation/perfusion ratios (McDonell, 1996).

The primary objective of this study was to investigate the hypoxaemic potential of a number of α_2 agonists possessing variable α_2/α_1 selectivity ratios following their i.v. administration at equipotent sedative doses in conscious sheep. The α_2 agonists compared in the present study are xylazine, romifidine, detomidine and medetomidine.

MATERIALS AND METHODS

Experimental animals and instrumentation

Five adult female Arcot sheep weighing between 63 and 80 kg (mean 69 $\pm$ 2.6 kg, SEM) were used in the study. Each animal was subjected to five experiments involving four α_2 agonists and a saline placebo, with a minimum of 7 days between experiments. The study was approved by the institutional Animal Care Committee, and the guidelines of the Canadian Council on Animal Care were followed throughout the study. At least 1 month prior to experimentation, the carotid artery was relocated to a subcutaneous position in all the animals under halothane anaesthesia. Health status of the animals was established on the basis of physical examination, a complete blood count, arterial blood gas analysis and thoracic radiography. Feed was withheld for 20–24 h before each experiment, with free access to water permitted.

To ensure that sedation did not produce a change in body position, the sheep were restrained in a custom designed wooden stock mounted on the frame of a portable trolley. The base of the wooden stock had four holes cut in it to permit protrusion of the legs. When in the restraint device, the sheep rested on their sternum and abdomen on a pad of foam 15 cm thick with their legs protruding through the holes. The device maintained a consistent head and neck position throughout the study. The sheep were conditioned to placement in the restraining device prior to the initial experiment by placing the animal in the device for 2 h every day for 7 days.

Using local analgesia (lidocaine 2%, Xylocaine; Astra Pharmaceuticals Inc., Missisaugua, ON, USA), a 20 gauge catheter (Angiocath; Deseret Medical Inc., Becton Dickinson, UT, USA) was introduced into the relocated carotid artery percutaneously to measure mean arterial pressure (MAP) and to collect arterial blood samples, while an 18 gauge catheter (Angiocath; Deseret Medical Inc., Becton Dickinson) was introduced into the external jugular vein for administration of drugs. The scapulohumeral joint was used as the zero reference point for MAP measurements. A base apex lead system of electrocardiography (ECG) was used for recording heart rate (HR) and rhythm using copper alligator clips attached to stainless steel wire loops placed subcutaneously under local analgesia. The MAP and ECG were recorded continuously using a five channel monitor (Criticare 1100 patient monitor; Criticare System Inc., Waukesha, WI, USA). Digital MAP values were entered into a computer using a frequency of 1.0 Hz operating on a program written in our laboratory. A total of 60 values were collected at each sampling interval (i.e. over 1 min) and were averaged to obtain a representative value for that sampling interval. The maximum change in transpulmonary pressure (ΔPpl) was estimated using a differential pressure transducer (Model MP 45–30871, S/N 20794, range $\pm$ 80 cm H_2O; Validyne Engineering Corp., Northridge, CA, USA) with one side of the transducer connected to the atmosphere and the other to a thin latex oesophageal balloon (7 cm long), affixed to the end of a 130 cm polyethylene catheter (2 mm i.d and 3 mm o.d). The oesophageal balloon was passed intranasally into the caudal third of the oesophagus using local analgesia (lidocaine viscous 2%; Pharma Science Inc., Montreal, QE, Canada). Throughout the experiment, the balloon volume was maintained at 1.5 mL of air. Frequency response of the transducer/catheter system was tested using the method of Young and Tesarowski (1994) and it was linear up to a frequency of 6 Hz. Respiratory rate was calculated manually from the analogue recording of ΔPpl over 1 min at each sampling interval. Arterial blood was collected anaerobically and stored on ice before analysis of blood gas and acid base values within 1 h of collection using an automated blood gas analyser (ABL 5000, Radiometer A/S; Bach-Simpson Ltd, Copenhagen, Denmark). The blood gas analyser was calibrated daily with reference liquid samples (Qualichek, Radiometer A/S; Bach-Simpson Ltd) and throughout the measurement period with precision gases. Blood gas values were corrected to body temperature. The alveolar oxygen tension (PAO_2) was calculated using the alveolar gas equation (Jones, 1987). The PaO_2 value was subtracted from the calculated value of PAO_2 to estimate the alveolar-to-arterial oxygen tension gradient, i.e. $P(A\text{-}a)O_2$.

Experimental design

The study was conducted using a randomized Latin square design with five i.v. treatments: 2.0 mL saline (placebo); xylazine (Rompun®, 20 mg/mL; Haver, Bayvet Division, Chemagro Ltd, Etobicoke, ON, Canada) at 150 μg/kg; romifidine (Sedivet®, 10 mg/mL; Boehringer Ingelheim, Burlington, ON, Canada) at 50 μg/kg; detomidine (Dormosedan®, 10 mg/mL; Orion Corporation, Farmos, Turku, Finland) at 30 μg/kg; and medetomidine (Domitor™, 1 mg/mL; Orion Corporation) at 10 μg/kg.

The dose of xylazine was the same as has been used in previous cardiopulmonary studies in our laboratory (Doherty *et al.*, 1986) where it produced an acceptable degree of sedation.

We selected 150 μg/kg, 50 μg/kg, 30 μg/kg and 10 μg/kg for xylazine, romifidine, detomidine and medetomidine as quasi-equipotent sedative doses based on a preliminary study (Celly *et al.* unpublished data). These doses were confirmed for sedative efficacy by administration of each drug to five animals with subsequent assessment of the degree of sedation based on the onset of recumbency, and the response to pinching of the digit and flank with haemostats and of a needle prick at the coronary band. The person responsible for assessment was blinded to the agent administered. At the quasi-equipotent sedative doses selected, the sheep became sternally recumbent shortly after administration and would remain in lateral recumbency when so positioned. However, if forced to stand up, the animals would move around. For 15–20 min, the sheep showed no response to pinching of the flank with a haemostat, a diminished response to needle pricking at the coronary bands and to the manual compression of the interdigital space.

After instrumentation, the sheep were given 15–20 min to assume an unstimulated baseline attitude. This was determined by the general demeanour of the sheep, HR and MAP. After achieving a steady baseline for at least 10 min, the drugs were administered i.v. at the equipotent sedative doses. Recordings and arterial blood samples were collected 2, 5, 10, 15, 20, 30, 45 and 60 min post drug administration.

Statistical analysis

The data collected over time were subjected to two way analysis of variance (ANOVA) for repeated measures to test for significance ($P \leqslant 0.05$) of the effect of treatment over time as well as for differences among treatments and the placebo group. When a significant effect of treatment or time was observed, comparisons were performed between treatments using one way ANOVA and a post hoc least significant difference (LSD) test. To account for repeated measures in the experimental design, the LSD was calculated using α values corrected by Bonferroni's method to control the overall level of significance ($P \leqslant 0.05$) (Dawson-Saunders & Trapp, 1990). The results have been presented as mean ± SEM.

RESULTS

All animals treated with α_2 agonists showed drooping of ears, eyelids and head, and diminished awareness of their surroundings within 30 s of drug administration and these signs lasted for ≈30 min. Thereafter, the animals showed increasing levels of alertness as they became aware of their surroundings. There was no evidence of sedation in the placebo treated animals and none of the measured variables changed over time with this treatment.

All α_2 agonists caused an initial period of apnoea which lasted for 30–60 s (Fig. 1). This was followed by a significant increase in the respiration rate by 2 min post drug administration (Fig. 2). The respiration rate increased to a maximum of 98.6, 99.2, 60.1 and 84 breaths/min with xylazine, romifidine, detomidine and medetomidine, respectively (as compared to the baseline respiratory rate of 15–16 breaths/min). When compared to the placebo treatment, xylazine and medetomidine produced an increase in respiratory rate from 2 to 30 min, romifidine increased the rate from 2 to 60 min, while detomidine increased it from 10 to 30 min.

All α_2 agonists treated groups showed an increase in ΔPpl over time; however, when compared to the saline treated group, only xylazine and romifidine showed a significant increase (Fig. 2). In romifidine treated sheep, the values remained significantly high throughout the length of the experiment. The ΔPpl values increased to 28.2 and 40.0 cm H_2O (as compared to the baseline ΔPpl value of 7–8 cm H_2O) with xylazine and romifidine, respectively.

A significant decrease in PaO_2 levels was seen in all drug treated groups within 2 min of drug administration, with the maximum decrease by 10 min (Fig. 3). Although the effect on PaO_2 levels was somewhat reduced towards the end of the study, even at 60 min post drug administration, PaO_2 levels were significantly lower. The minimum levels of mean PaO_2 were 32.6 mm Hg, 29.7 mm Hg, 42.1 mm Hg and 38.7 mm Hg (4.3 kPa, 3.9 kPa, 5.6 kPa and 5.1 kPa) with xylazine, romifidine, detomidine and medetomidine, respectively. Despite the significant drop in PaO_2 levels, no changes in the $PaCO_2$ values were

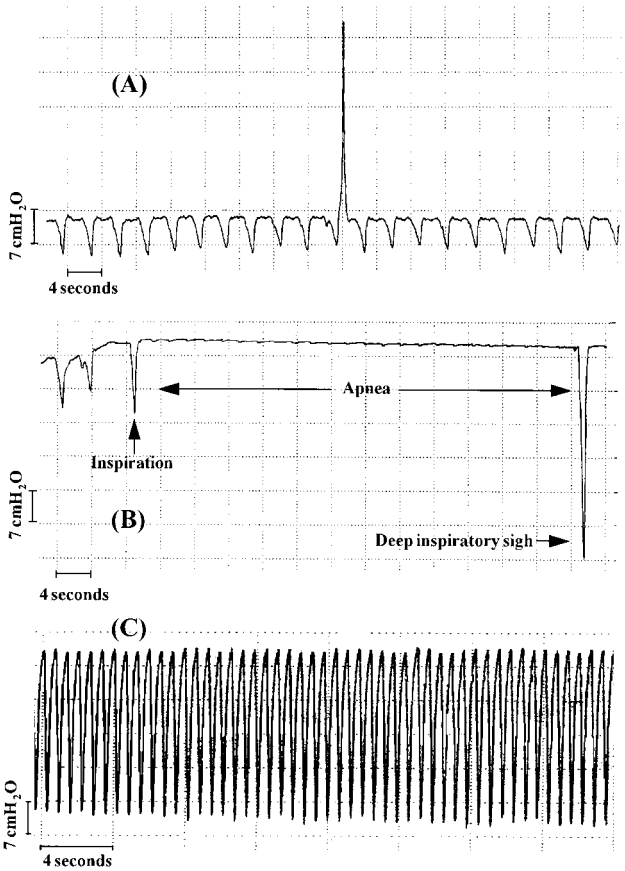

Fig. 1. Representative trace showing: (A) the respiratory rhythm before drug administration. The single positive deflection was produced by oesophageal contraction after a swallowing movement; (B): a period of apnoea immediately following administration of xylazine at 150 μg/kg, i.v. Intermittent deep sighs interrupting the period of apnoea are also seen; (C): the increased respiratory frequency and pleural pressure swings 30 s following administration of xylazine at 150 μg/kg, i.v, in another sheep.

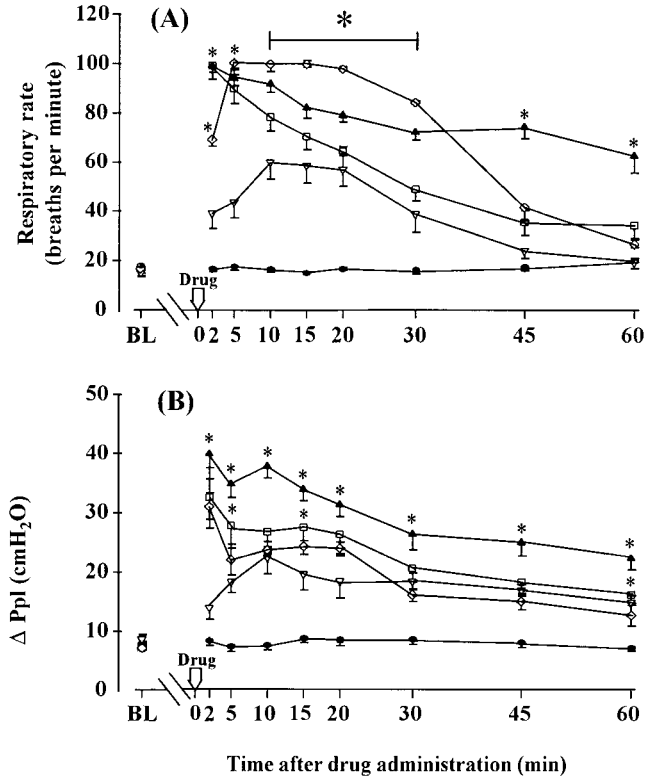

Fig. 2. Comparative changes in (A) mean respiratory rate and (B) maximum change in transpulmonary pressure, ΔPpl; after i.v. administration of an α_2 agonist or placebo. Baseline (BL) values and response over 60 min are shown for placebo (●), xylazine (□, 150 μg/kg), romifidine (▲, 50 μg/kg), detomidine (▽, 30 μg/kg) and medetomidine (◇, 10 μg/kg). Significant differences ($P \leqslant 0.05$) between placebo and an individual α_2 agonist response are shown (*), as well as where all four agents differ from the placebo treatment (⊢*⊣). Each data point represents the mean and SEM of five animals. The statistical significance was established by Least significance difference test with Bonferroni's correction.

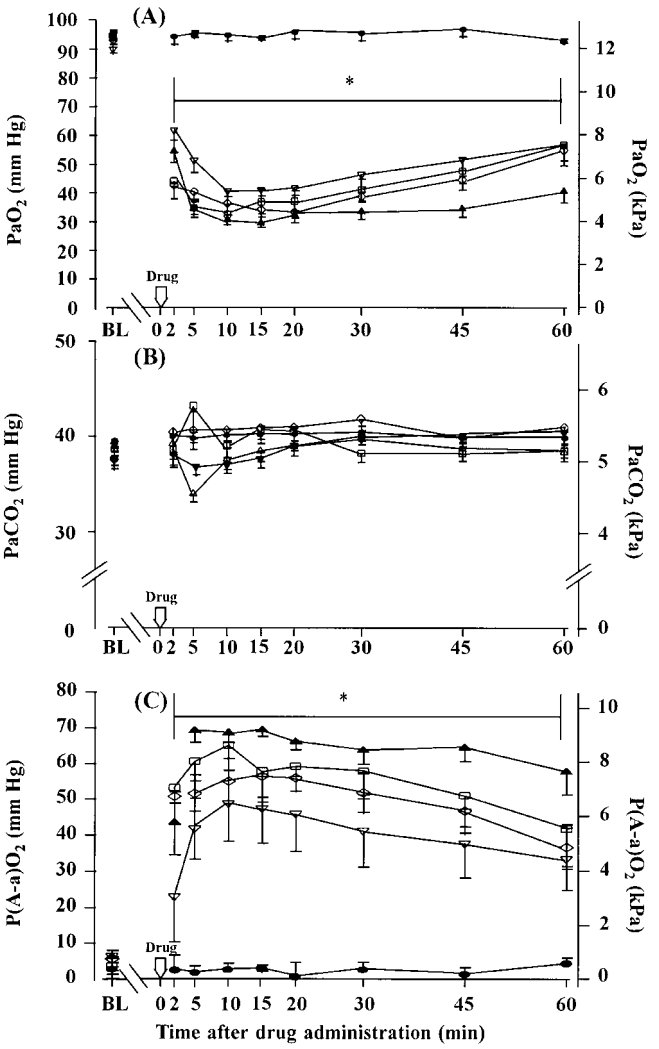

Fig. 3. Comparative changes in (A) PaO_2 (B) $PaCO_2$, and (C) $P(A\text{-}a)O_2$ after i.v. administration of an α_2 agonist or placebo. Baseline (BL) values and response over 60 min are shown for placebo (●), xylazine (□, 150 μg/kg), romifidine (▲, 50 μg/kg), detomidine (▽, 30 μg/kg) and medetomidine (◇, 10 μg/kg). Significant differences ($P \leqslant 0.05$) where all four agents differ from the placebo treatment are shown (⊢*⊣). Each data point represents the mean and SEM of five animals. The statistical significance was established by Least significance difference test with Bonferroni's correction.

observed with any treatment (Fig. 3). Significant increases were seen in $P(A\text{-}a)O_2$ in all the α_2 agonist treated groups (Fig. 3). No significant changes were seen in arterial blood pH and base excess values from the α_2 agonist treated animals compared to the saline treated group.

In general, haemodynamic variables such as MAP and HR showed more variations between drugs and between animals than the respiratory variables. As compared to the saline treated group, a significant increase in MAP was observed up to 10 min after administration of romifidine and detomidine, however, a significant decrease was seen at 10 and 45 min after xylazine and medetomidine, respectively (Table 1).

Except for xylazine, all α_2 agonists studied tended to decrease HR throughout the study. The HR decreased significantly at 2 min after romifidine, detomidine and medetomidine treatment, and remained lower until 10 min with detomidine. Except for sinus arrhythmia in one xylazine treated animal, no other conduction defects were seen.

All α_2 agonists produced approximately the same degree of hypoxaemia. Statistical analysis of the drug responses at 5, 30 and 60 min confirmed that they were not different (Table 2). Significant variations were seen between different α_2 agonists for some of the other variables at some time periods (Table 2).

DISCUSSION

The pretreatment (baseline) values for all measured variables were within normal limits for sheep (McDonell, 1996). These observations indicate that the sheep were healthy and calm at the time of administration of the drugs, and that arterial oxygenation was not being affected by positioning of the sheep in the restraint device. No significant changes were observed over

Table 1. Effect of i.v. administration of placebo, xylazine, romifidine, detomidine and medetomidine on mean arterial pressure (MAP) and heart rate (HR) in conscious sheep*

Variable	Treatment ($n = 5$)[a]	Time post-drug administration (min)							
		Baseline	2	5	10	15	20	30	45	60
MAP (mm Hg)	PLA	109.3 ± 3.3	109.8 ± 3.6	114.9 ± 1.6	112.9 ± 4.1	113.3 ± 2.2	114.1 ± 2.4	108.5 ± 1.5	114.7 ± 2.3	109.4 ± 2.0
	XYL	109.6 ± 3.1	113.9 ± 12.3	102.2 ± 8.6	88.4 ± 6.4[b]	101.3 ± 11.4	87.9 ± 5.7	92.9 ± 10.5	83.3 ± 2.4	89.3 ± 3.2
	ROM	112 ± 2.6	157.6 ± 6.9[b]	152.1 ± 4.1[b]	143.1 ± 5.0[b]	137.6 ± 3.6	126.0 ± 5.4	117.5 ± 4.3	105.1 ± 5.0	94.2 ± 6.3
	DET	105.7 ± 3.8	143.9 ± 4.1[b]	140.4 ± 10.3[b]	139.3 ± 5.6[b]	133.6 ± 6.3	128.9 ± 7.2	123.6 ± 6.2	111.5 ± 4.2	103.6 ± 4.0
	MED	111.25 ± 1.8	132.1 ± 4.0	126.6 ± 4.6	122.0 ± 6.8	116.6 ± 7.0	102.9 ± 11.4	97.2 ± 11.0	85.6 ± 4.7[b]	91.9 ± 2.5
HR (beats per minute)	PLA	81.7 ± 3.3	80.6 ± 4.8	81.9 ± 4.1	79.1 ± 3.6	86.3 ± 11.1	77.7 ± 6.3	82.6 ± 5.6	81 ± 1.9	75.4 ± 3.2
	XYL	86.6 ± 6.4	50.4 ± 10.8	75.7 ± 25.0	83.3 ± 14.2	88.1 ± 17.3	84.8 ± 15.4	59.8 ± 6.2	57.1 ± 6.4	62.2 ± 3.5
	ROM	83.3 ± 4.1	28.2 ± 5.7[b]	41.4 ± 4.5	53.4 ± 7.1	55.8 ± 6.7	56.7 ± 6.1	60.0 ± 7.4	65.8 ± 10.6	77.7 ± 14.6
	DET	84.6 ± 6.2	36.3 ± 9.2[b]	33.2 ± 5.4[b]	37.2 ± 3.1[b]	48.7 ± 4.9	49.6 ± 5.3	50.3 ± 5.6	55.1 ± 7.1	61.6 ± 9.5
	MED	79.9 ± 8.7	40.3 ± 6.4[b]	38.5 ± 4.4	46.0 ± 7.3	54.4 ± 8.2	58.6 ± 6.2	68.6 ± 6.8	68.8 ± 8.4	54.9 ± 5

*Values expressed as Mean ± SEM. [a]PLA: placebo, XYL: xylazine (150 μg/kg), ROM: romifidine (50 μg/kg), DET: detomidine (30 μg/kg), MED: medetomidine (10 μg/kg). [b]Significantly different from placebo group ($P \leqslant 0.05$) (Least significance difference test with Bonferroni's correction).

Table 2. Statistical comparison of effect of different α_2 agonists on various cardiopulmonary variables

Variables*	Time after drug administration		
	5 min	30 min	60 min
PaO_2 (mm Hg)			
PLA	95.2 ± 2.0[a]	94.4 ± 2.4[a]	92.8 ± 1.3[a]
XYL	34.8 ± 4.9[b]	41.1 ± 6.7[b]	56.9 ± 9.6[b]
ROM	34.7 ± 4.0[b]	33.6 ± 3.7[b]	40.8 ± 6.6[b]
DET	50.2 ± 4.8[b]	49.0 ± 5.0[b]	57.1 ± 6.2[b]
MED	43.7 ± 4.5[b]	43.1 ± 4.5[b]	59.3 ± 7.2[b]
RR (breaths/min)			
PLA	16.8 ± 1.0[a]	15.3 ± 0.4[a]	18.9 ± 1.4[a]
XYL	79.8 ± 13.3[b]	45.0 ± 7.8[b,c]	30.6 ± 9.4[b]
ROM	94.2 ± 5.9[b]	72.5 ± 4.9[b]	62.8 ± 11.2[b]
DET	43.8 ± 10.7[a]	39.1 ± 12.5[a,c]	19.5 ± 2.8[a]
MED	84.0 ± 11.5[b]	67.3 ± 11.6[b,c]	22.6 ± 3.6[b]
DPpl (cm H_2O)			
PLA	7.4 ± 0.9[a]	8.6 ± 0.9[a]	7.2 ± 0.4[a]
XYL	24.8 ± 6.8[b,c]	18.2 ± 4.5[a,b]	15.1 ± 2.5[b]
ROM	34.9 ± 3.6[b]	26.5 ± 4.2[b]	22.4 ± 3.0[c]
DET	16.2 ± 3.2[a,b]	16.5 ± 2.9[a,b]	13.7 ± 2.2[a,b]
MED	20.1 ± 4.5[a,b,c]	16.3 ± 1.4[a,b]	11.9 ± 2.7[a,b]
MAP (mm Hg)			
PLA	114.9 ± 1.6[a,b]	108.5 ± 1.5[a]	109.4 ± 2.0[a]
XYL	102.2 ± 8.6[b]	92.9 ± 10.5[a]	89.3 ± 3.2[a]
ROM	152.1 ± 4.1[c]	117.5 ± 4.3[a]	94.2 ± 6.3[a]
DET	140.4 ± 10.3[c]	123.6 ± 6.2[b]	103.6 ± 4.0[a]
MED	126.6 ± 4.6[a,b,c]	97.2 ± 11.0[a]	91.9 ± 2.5[a]
HR (beats/min)			
PLA	81.9 ± 4.1[a]	82.6 ± 5.6[a]	75.4 ± 3.2[a]
XYL	75.7 ± 25.0[a]	59.8 ± 6.2[b]	62.2 ± 3.5[a]
ROM	41.4 ± 4.5[a]	60.0 ± 7.4[b]	77.7 ± 14.6[a]
DET	33.2 ± 5.4[b]	50.3 ± 5.6[b]	61.6 ± 9.5[a]
MED	38.5 ± 4.4[a]	68.6 ± 6.8[a,b]	54.9 ± 5.0[a]

*PaO_2: partial pressure of oxygen in arterial blood; RR: respiratory rate; ΔPpl: maximum change in the transpulmonary pressure; HR: heart rate; MAP: mean arterial pressure.

Treatments: PLA: placebo; XYL: xylazine; ROM: romifidine; DET: detomidine; MED: medetomidine. ($n = 5$ for each treatment).

Similar letters denote no significant difference between treatments ($P \leqslant 0.05$). (Least significance difference with Bonferroni's correction).

time for any variable in the saline treated animals, indicating that the restraint device was well tolerated by the animals over the time period required for instrumentation and completion of the study (90–120 min).

Respiration and gas exchange

The main finding of the study was the development of significant and profound hypoxaemia (PaO_2 levels < 50 mm Hg or 6.6 kPa) following administration of all of the α_2 agonists studied (Fig. 3). The decrease in PaO_2 levels in the present study was comparable to decreases observed previously with xylazine (Doherty *et al.*, 1986; Hsu *et al.*, 1989), clonidine (Eisenach, 1988), or more recently with medetomidine (Bryant *et al.*, 1996). Waterman and colleagues (Waterman *et al.*, 1987) observed less profound hypoxaemia (mean PaO_2 55–60 mm Hg or 7.3–7.9 kPa 5 min post drug administration) with lower doses of xylazine (50 μg/kg) or detomidine (10 μg/kg). In the present study, the hypoxaemia produced by each of the four drug treatments was similar in terms of the degree of PaO_2 depression and the time of onset and recovery. At the doses studied, detomidine tended to produce the least decrease in PaO_2, with less tachypnoea and increase in ΔPpl, but this difference was not statistically significant. The similarity of the hypoxaemic responses at quasi-equipotent sedative doses occurred even though there is a 7–10 fold greater selectivity of detomidine and medetomidine for α_2 over α_1 adrenoceptors vs. xylazine (Virtanen *et al.*, 1988). The close relationship between the α_2 agonist-induced sedation and the degree of hypoxaemia appears to point to a primary α_2 agonist cause, rather than an effect on another receptor such as an α_1. This finding is supported by the observation that xylazine induced hypoxaemia in sheep is prevented by pretreatment with the α_2 adrenoceptor antagonist idazoxan (Nolan *et al.*, 1986; Waterman *et al.*, 1987), and not with the α_1 adrenoceptor antagonist prazosin (Nolan *et al.*, 1986).

In contrast, when the α_2 antagonist yohimbine was administered 5 (Hsu *et al.*, 1989) or 20 min (Doherty *et al.*, 1986) after xylazine administration, the sedative effect was reversed, but not the hypoxaemia. When the more selective α_2 antagonist

idazoxan was given 5 min after xylazine, the reversal of sedation in sheep was rapid and complete, while the reversal of the hypoxaemia was partial and prolonged (Hsu *et al.*, 1989).

It is apparent from the findings of the present study that the hypoxaemia is not due to hypoventilation as there was no increase in $PaCO_2$ after treatment with any of the α_2 agonists studied. This is in agreement with earlier observations of the respiratory response to xylazine sedation in sheep (Doherty *et al.*, 1986; Waterman *et al.*, 1987; Hsu *et al.*, 1989), although an increase in $PaCO_2$ has been reported after medetomidine (Bryant *et al.*, 1996).

As the sheep in the present study did not undergo a change in body position after the onset of sedation, body position can be eliminated as a cause of the hypoxaemia. Positional change, or the initial body position, was a confounding factor in most of the previous studies involving the ruminant response to α_2 agonist induced sedation (Mitchell & Williams, 1977; Doherty *et al.*, 1986; Hsu *et al.*, 1989; Bryant *et al.*, 1996). In other studies, it is not clear whether a positional change was involved (Eisenach, 1988), or if the dose of α_2 agonist administered was less than a sedative dose (Waterman *et al.*, 1987). In sheep (Hedenstierna *et al.*, 1989), as in other species (Nunn, 1985; Jones *et al.*, 1990; Nyman *et al.*, 1990), recumbency and sedation/anaesthesia leads to pulmonary atelectasis and an associated impairment of pulmonary gas exchange (McDonell, 1996).

The increase in $P(A\text{-}a)O_2$ is essentially a mirror image of the decrease in PaO_2, and provides a measure of the degree of pulmonary venous admixture that is occurring subsequent to administration of the α_2 agonists. This increase in venous admixture is potentially due to an increase in the scatter of ventilation/perfusion ratios within regional areas of the lung, or it might be because of an increase in right-to-left pulmonary shunt flow or a fall in cardiac output and the oxygen tension in the mixed venous (pulmonary artery) blood (Nunn, 1985; McDonell, 1996). Nolan *et al.* (1986) reported hypoxaemia after i.v. administration of xylazine (20 μg/kg) in sheep anaesthetized with halothane and ventilated with a mixture of oxygen and nitrous oxide. These authors suggested that an increase in the shunt fraction was the most likely cause of α_2 agonist induced hypoxaemia. An increase in the shunt fraction could theoretically occur because of the development of segmental airway obstruction, pulmonary oedema or atelectasis, or opening up of the previously closed vascular connections between the right side of the circulation and the left side (McDonell, 1996).

While the increase in ΔPpl was only significant for xylazine and romifidine at the level of significance selected, there was considerable increase in the mean ΔPpl values after medetomidine at 10 min. An increase in airway pressure (trachea to atmosphere) in anaesthetized and ventilated sheep following i.v. administration of xylazine at 20 μg/kg and 0.2 mg/kg was reported by Nolan *et al.* (1986) and Papazoglou *et al.* (1994), respectively. An increase in airway pressure during intermittent positive pressure ventilation may be due either to a change in pulmonary mechanics, or to a change in chest wall mechanics, or both. In the present study, transpulmonary pressure (mouth to pleural space, i.e. oesophagus) was measured and, as such, the increase in ΔPpl observed after the administration of the four α_2 agonists is strongly suggestive of a pulmonary parenchymal origin for the increase in $P(A\text{-}a)O_2$ and decrease in PaO_2. The increase in ΔPpl is generally associated with an alteration of pulmonary mechanics (non-elastic work of breathing, pulmonary resistance and dynamic compliance) (Tesarowski *et al.*, 1996), the only exception being if there is a large increase in tidal volume or upper airway resistance. As precautions were taken to minimize any change in head and neck position subsequent to the administration of the α_2 agonists in the present study, it is unlikely that there was a large change in upper airway resistance (Lavoie *et al.*, 1992). Given that there was a large increase in respiratory frequency after administration of the α_2 agonists and that $PaCO_2$ levels did not change, it also seems very unlikely that the tidal volume increased, although no measurements of tidal volumes were obtained.

While an increase in ΔPpl indicates a change in pulmonary mechanics, it does not specify the origin, i.e. whether it occurred due to a decrease in compliance, an increase in resistance, or both. To date, no study on the effect of α_2 agonists on respiratory mechanics is available in sheep; however, a marked increase in resistance following i.v. administration of xylazine (20 μg/kg) was reported in calves (Gustin *et al.*, 1989).

In addition to the increase in ΔPpl, a significant increase in respiratory rate was also seen following administration of the four drugs. The increase in respiratory rate might have been a response to the low PaO_2 levels (Boggs, 1992), or to an increase in the pulmonary resistance. The usual respiratory pattern response to a decrease in compliance is to increase the frequency and decrease tidal volume (Peters, 1968; Otis, 1986), so as to decrease the minute work of breathing.

It is interesting to note in our study that the duration of hypoxaemia outlasted the duration of sedation. This finding suggests that sedation, *per se*, may not play a major role in the α_2 agonist induced hypoxaemia and that, while both sedation and hypoxaemia appear to be mediated by α_2 adrenoceptors, the kinetics of the drug receptor interaction appears to be quite different.

Cardiovascular variables

Following xylazine administration, no significant decrease in MAP was seen except at 10 min, when a significant decrease was observed compared to control animals. The pressor response of xylazine was similar to the earlier studies using i.v. xylazine (150 μg/kg) in conscious sheep, where a non-significant decrease in MAP was seen (Doherty *et al.*, 1986). In contrast to xylazine, medetomidine, romifidine and detomidine showed a biphasic pressor response, i.e. an initial hypertension (not significant in the case of medetomidine) followed by an eventual return to normal blood pressure, or in the case of medetomidine a significant decrease at 45 min.

There are no studies on the pressor response to detomidine and romifidine administration in sheep. Medetomidine produced a dose related biphasic pressor response, along with bradycardia and a significant decrease in cardiac output (Bryant *et al.*, 1996). A biphasic pressor response following i.v. administration of α_2

agonists is considered as the classical pressor response in normotensive subjects (Ruffolo *et al.*, 1993). The initial hypertensive response is mediated by stimulation of peripheral arterial post junctional α_1 and α_2 adrenoceptors and is usually short lived. This is followed by a slow decline in arterial blood pressure due to central α_2 adrenoceptor stimulation, which induces a reduction in sympathetic outflow to the periphery, and vagally induced bradycardia (Kobinger, 1978; Van Zwieten *et al.*, 1983). In the present study, the initial hypertensive response following detomidine and romifidine was long lasting. A similar long lasting hypertension has also been reported following dexmedetomidine, a dextro-rotatory isomer of medetomidine, in conscious (Schmeling *et al.*, 1991) and isoflurane anaesthetized (Bloor *et al.*, 1992) dogs. While explaining the sustained hypertensive response following dexmedetomidine administration, Schmeling *et al.* (1991) proposed that dexmedetomidine is less efficacious at those imidazoline binding sites in the central nervous system (CNS) which mediate sympatholytic (hypotensive) effects. This could partially explain the sustained hypertension in the present study, however, no study on the difference in efficacy of dexmedetomidine on different imidazoline binding sites within the CNS have been done.

Another factor which might have contributed to differences observed in the cardiovascular responses of the different α_2 agonists in the present study is our criteria of dose selection. The criteria for dose selection was a comparable sedation, as judged by a subjective scoring system. As such, the equipotent sedative doses used in the present study should better be termed 'quasi-equipotent' rather than 'true equipotent'. This might have influenced the cardiovascular response of the drugs; however, it is interesting to note that no such influence was seen on the hypoxaemic response of the different α_2 agonists. It is also possible that the severe hypoxaemic state induced by the α_2 agonists induced a release of endogenous catecholamines, thereby secondarily affecting the cardiovascular response.

A significant decrease in HR was seen within 2 min of romifidine, detomidine and medetomidine administration. Xylazine treated animals also showed a decrease in HR, but the decrease was not significant. These findings are also in accordance with various earlier studies where a bradycardic response was reported following i.v. administration of xylazine (Doherty *et al.*, 1986), clonidine (Eisenach, 1988), detomidine (Clark *et al.*, 1993) and medetomidine (Ko & McGrath, 1995; Bryant *et al.*, 1996) in sheep. A significant drop in HR is considered the classic response after administration of α_2 agonists in all animal species tested (Ruffolo *et al.*, 1993). Activation of α adrenoceptors in the brain enhances vagally induced bradycardia resulting from increased arterial pressure or from stimulation of the carotid sinus nerve (Robson *et al.*, 1969; Kobinger & Walland, 1971; Antonaccio *et al.*, 1973). However, this does not completely explain our findings as a decrease in HR was always seen, irrespective of whether the agonist produced hypertension or not. Nonetheless, enhanced vagal tone remains the most likely explanation for the bradycardia as α_2 adrenoceptors have been identified in the dorsal vagal nucleus, where they can be stimulated to enhance vagal outflow (Dashwood *et al.*, 1985). Further evidence in support of this hypothesis comes from the study of Bloor *et al.* (1992) where bradycardia induced by dexmedetomidine was abolished by prior administration of glycopyrrolate, an anticholinergic agent (Bloor *et al.*, 1992). In addition to the central action of α_2 agonists, peripheral effects of these drugs are also considered to have a role in bringing about bradycardia (DeJonge *et al.*, 1982). These authors suggested that the α_2 agonist-induced bradycardia was initiated by stimulation of peripheral presynaptic α_2 adrenoceptors in the heart at low doses, producing a maximum effect of about a 15% decrease in HR. However, if the drug can cross the blood brain barrier, it can stimulate central α_2 adrenoceptors resulting in an additional (predominantly vagally mediated) bradycardia. Decrease in HR has been reported following administration of an α_2 agonist which does not cross the blood brain barrier, i.e. ST-91 (Scriabine *et al.*, 1977). This observation supports the importance of a peripheral contribution to the bradycardic effects of α_2 agonists.

In conclusion: (1) the α_2 agonists used in this study showed comparable degrees of hypoxaemia despite their reported variable α_2/α_1 adrenoceptor selectivities; (2) the hypoxaemia seems to be associated with significant changes in the ΔPpl and respiratory rate; and (3) the hypoxaemia does not appear to be due to change in body position or sedation seen following α_2 agonists administration. The effect of these drugs on cardiac output can also contribute to hypoxaemia. This question was not addressed in the present study, however no marked change in the cardiovascular variables such as MAP and HR was observed. While only female sheep were studied in the present study, our own clinical experience using α_2 agonists for sedation in sheep, and that of others (Nolan *et al.*, 1990), does not suggest there is a sex predilection for a hypoxaemic response.

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