Cardiopulmonary effects of clonidine, diazepam and the peripheral α_2 adrenoceptor agonist ST-91 in conscious sheep

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The cardiopulmonary effects of the intravenous administration of clonidine (15 µg/kg), ST-91 (30 µg/kg) and diazepam (0.4 mg/kg) were compared in five healthy sheep using a randomized cross-over design, to determine whether the hypoxaemic effects of α_2 adrenoceptor agonists are due to sedation, or to peripheral α_2 adrenoceptor stimulation. All three drugs significantly lowered arterial oxygen tension (PaO_2) levels within 2 min of their administration; however, clonidine and ST-91 produced long lasting and severe hypoxaemia with mean PaO_2 levels of ≈ 40 mm Hg and 50 mm Hg (5.3 kPa and 6.6 kPa), respectively. The fall in PaO_2 was considerably less with diazepam (63 mm Hg or 8.4 kPa at 2 min) and by 15 min the values did not differ from placebo treated animals. None of the drugs increased arterial carbon dioxide tension ($PaCO_2$) levels when compared to saline treatment and the acid base variables did not show any significant change. A significant increase was recorded in the packed cell volume of the ST-91 treated group throughout the study. Within 2 min of their administration, all drugs caused a significant increase in mean arterial pressure (MAP) as compared to the placebo treated group. The MAP remained significantly increased for 5 and 60 min after clonidine and ST-91 treatment, respectively. The study shows that ST-91 and clonidine produce a greater degree of hypoxaemia than occurs with diazepam sedation, and that the hypoxaemic effect of α_2 adrenoceptor agonists in sheep are mainly mediated by peripheral α_2 adrenoceptors.

INTRODUCTION

The α_2 adrenoceptor agonists (α_2 agonists) are commonly used sedative analgesic agents in veterinary practice involving domestic as well as wild animal species (Adetunji *et al.*, 1984; Doherty & Tweedie, 1989). Although they produce excellent sedation and analgesia, a severe degree of hypoxaemia is seen following their administration at both sedative and non-sedative doses in sheep (Doherty *et al.*, 1986; Nolan *et al.*, 1986; Bryant *et al.*, 1996). In an earlier study (Celly *et al.*, 1997), it was found that a number of α_2 agonists possessing variable α_2/α_1 adrenoceptor selectivity ratios produced comparable degrees of hypoxaemia when administered intravenously (i.v.) to sheep at quasi-equipotent sedative doses. The hypoxaemia was characterized by an increase in the maximum change in transpulmonary pressure (ΔPpl) without a concomitant increase in $PaCO_2$, and occurred even when there was no change in body position. Others have reported that hypoxaemia induced by α_2 agonists persists even when the animal is ventilated with oxygen, suggesting there is an increase in intrapulmonary shunt fraction (Nolan *et al.*, 1986).

There is evidence that the hypoxaemic response of α_2 agonists in sheep is primarily brought about by α_2 adrenoceptor stimulation. Pretreatment with the α_1 antagonist idazoxan prevented the development of hypoxaemia (Waterman *et al.*, 1987), while pretreatment with the α_1 adrenoceptor antagonist prazosin did not (Nolan *et al.*, 1986). Eisenach (1988) observed a dose related decrease in PaO_2 levels in conscious sheep treated with the experimental drug, ST-91, an α_2 agonist that does not cross the blood brain barrier or produce sedation (Scriabine *et al.*, 1977).

In addition to sedation and analgesia, α_2 agonists also produce considerable muscle relaxation (Knight, 1980; Tranquilli & Maze, 1993). In small ruminants recumbency is usually produced with sedative doses (Mitchell & Williams, 1977; Kokkonen & Eriksson, 1987; Hsu *et al.*, 1989; Bryant *et al.*, 1996). It is possible that the degree of sedation and muscle relaxation is sufficient to alter the shape and/or function of the chest wall and diaphragm, thereby producing a change in the
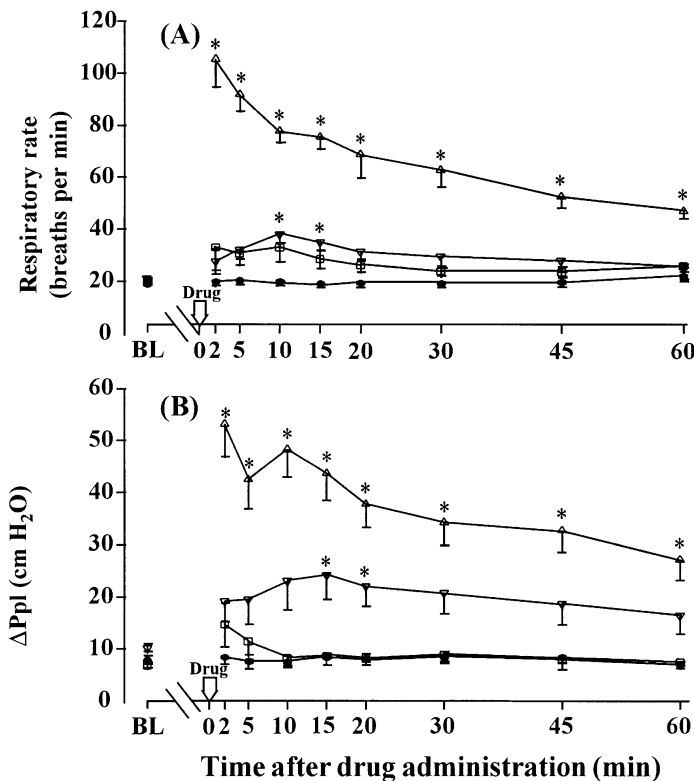
Fig. 1. Comparative changes in (A) mean respiratory rate and (B) maximum change in transpulmonary pressure, ΔPpl, after administration of different treatments. Baseline (BL) values and response over 60 min are shown for diazepam (□, 0.4 mg/kg), clonidine (△, 15 μg/kg), ST-91 (▽, 30 μg/kg) and placebo (●). Significant differences ($P \leqslant 0.05$) between the drugs and placebo are shown (*). The statistical significance was established by Least significance difference test with Bonferroni's correction.

distribution of inspired gas and matching of ventilation to perfusion throughout the lungs, as occurs during anaesthesia (Froese, 1985; Rehder, 1985; Benumof, 1994). In standing, conscious cattle ruminal insufflation produced impairment of pulmonary function, presumably through altered diaphragmatic position and function (Musewe *et al.*, 1979).

To explore the role of central sedation and chest wall muscle relaxation in α_2 agonist-induced hypoxaemia, the effect of clonidine and diazepam were compared in sheep. These two drugs were compared because they act on different receptor types but bring about clinically similar central effects. Clonidine produces sedation and muscle relaxation by interacting with central α_2 adrenoceptors (Timmermans *et al.*, 1983), whereas diazepam brings about sedation and muscle relaxation by interaction with γ-aminobutyric acid (GABA) receptors and glycine-mediated inhibitory pathways, respectively (Klein & Klide, 1989). Diazepam is an effective sedative in sheep and goats, and it produces considerable muscle relaxation (Gray & McDonell, 1986). In addition, the hypoxaemic potential of clonidine and the peripheral acting α_2 agonist, ST-91, were compared using an experimental preparation wherein alterations of body position were prevented.

MATERIALS AND METHODS

Five adult female Arcot sheep weighing between 63 and 80 kg (mean 69 ± 2.6 kg, SEM) were used in a randomized cross-over design. At least 1 month prior to experimentation, the carotid

artery was relocated subcutaneously 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, thoracic radiography and electrocardiographic examination. Feed was withheld for 20–24 h before each experiment, with free access to water. The animals were restrained and catheters were inserted to measure arterial blood pressure and transpulmonary pressure, as described elsewhere (Celly *et al.*, 1997). Each animal was subjected to four experiments involving three drugs: diazepam (Sabex®, 5 mg/mL; Sabex Inc., Boucherville, QE, Canada) at 0.4 mg/kg (Thurmon & Benson, 1993); clonidine (Boehringer Ingelheim, Burlington, ON, Canada) at 15 μg/kg (Eisenach, 1988); ST-91 (Boehringer Ingelheim) at 30 μg/kg (Eisenach, 1988) and a saline placebo, all administered i.v., with a minimum of 7 days between experiments.

The experimental methods, sampling intervals and data analysis were as outlined previously (Celly *et al.*, 1997). 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 between 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 $\pm$ SEM.
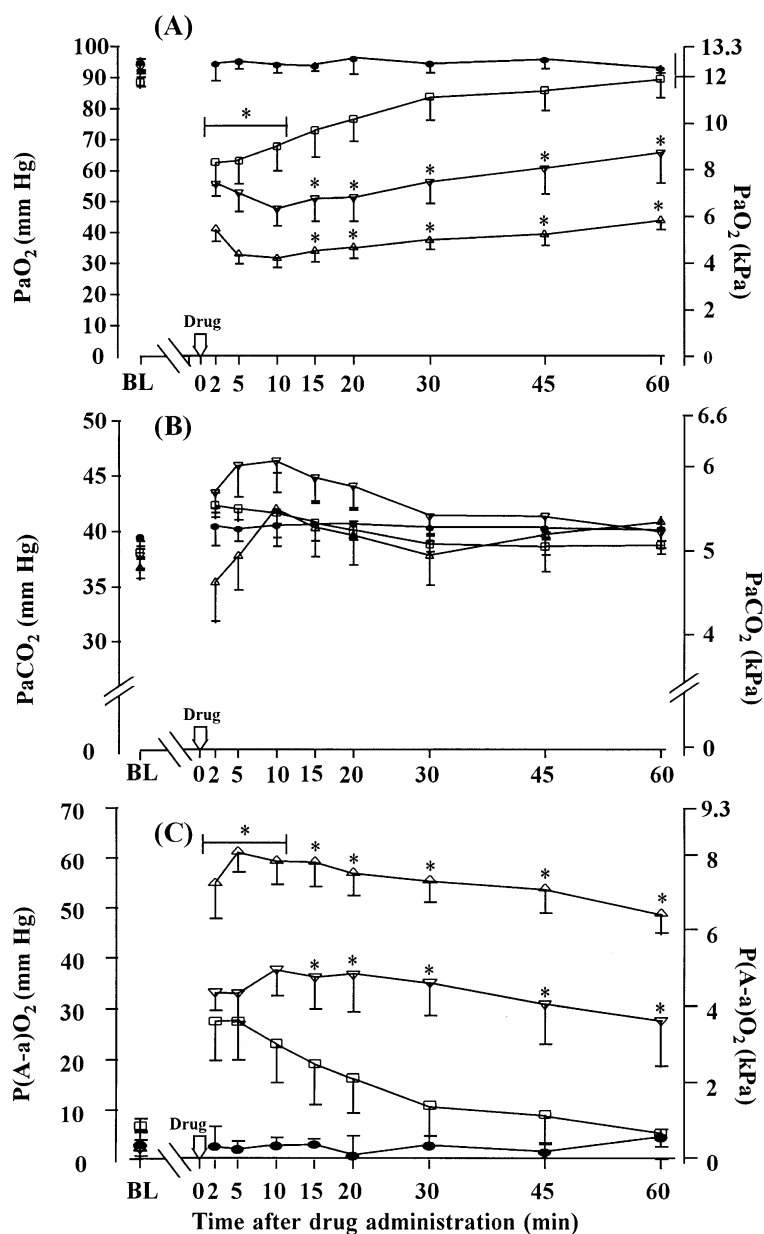
Fig. 2. Comparative changes in (A) PaO_2, (B) $PaCO_2$ and (C) $P(A-a)O_2$ after administration of different treatments. Baseline (BL) values and response over 60 min are shown for diazepam ($\square$, 0.4 mg/kg), clonidine ($\triangle$, 15 µg/kg), ST-91 ($\triangledown$, 30 µg/kg) and placebo ($\bullet$). Significant differences ($P \leqslant 0.05$) between different treatments and placebo are shown (*), as well as where all three agents differ from the placebo treatment ($\vdash$—*—$\dashv$). The statistical significance was established by Least significance difference test with Bonferroni's correction.

RESULTS

Behavioural changes

Animals treated with clonidine and diazepam showed a rapid onset of sedation, which lasted ≈ 30 and 25 min, respectively. Animals treated with ST-91 were not sedated, but did demonstrate slight drowsiness. No behavioural change was noticed in the saline treated animals, and there was no significant change in any other variable with this treatment.

Respiration and gas exchange

Following administration of clonidine and ST-91, there was a brief period of apnoea lasting not more than 45 s. This was interrupted by deep sighs, followed by an increased respiratory rate similar to that observed earlier with other α_2 agonists (Celly et al., 1997). Although all three drugs tended to increase respiratory rate, the increase caused by diazepam was of less magnitude and was not significant at the significant level chosen (from a baseline value of 16.6–29.6 breaths/min). The maximum increase with ST-91 was also modest (from 16.4–34.7 breaths/min) and was significant only at 10 and 15 min after administration, whereas the change was marked and significant throughout the study period with clonidine (from 17.2–102.3 breaths/min) (Fig. 1). No significant change was seen in ΔPpl values in diazepam treated animals, whereas a significant increase was seen after clonidine for up to 60 min. The ΔPpl values with ST-91 treatment were also significantly elevated at 15 and 20 min (Fig. 1).

All three drugs significantly lowered PaO_2 levels by 2 min after their administration; however, the extent and duration of the

Table 1. Statistical comparison of effect of placebo, diazepam, clonidine and ST-91 on various cardiopulmonary variables

Variables*	Time after drug administration		
	5 min	30 min	60 min
PaO_2 (mmHg)			
PLA	95.2 ± 2.0^a	94.4 ± 2.4^a	92.8 ± 1.3^a
DIAZ	63.3 ± 7.2^b	83.9 ± 7.2^a	89.6 ± 5.8^a
CLON	33.2 ± 2.7^b	37.6 ± 2.5^b	44.0 ± 2.7^b
ST-91	52.9 ± 5.7^b	56.4 ± 6.8^b	65.7 ± 9.4^b
RR (breaths/min)			
PLA	16.8 ± 1.0^a	15.3 ± 0.4^a	18.9 ± 1.4^a
DIAZ	27.4 ± 4.3^a	20.6 ± 1.8^a	22.6 ± 0.7^a
CLON	88.7 ± 6.3^b	59.4 ± 6.1^b	43.7 ± 2.4^b
ST-91	28.8 ± 3.7^a	26.0 ± 4.4^a	21.8 ± 3.9^a
ΔPpl (cm H_2O)			
PLA	7.4 ± 0.9^a	8.6 ± 0.9^a	7.2 ± 0.4^a
DIAZ	11.5 ± 2.6^a	8.9 ± 1.2^a	7.6 ± 1.0^a
CLON	42.6 ± 5.3^b	34.4 ± 4.3^b	27.2 ± 3.7^b
ST-91	19.7 ± 4.7^a	20.9 ± 3.8^a	16.6 ± 3.4^a
MAP (mm Hg)			
PLA	114.9 ± 1.6^a	108.5 ± 1.5^a	109.4 ± 2.0^a
DIAZ	131.4 ± 3.8^a	115.7 ± 3.9^a	119.5 ± 2.8^a
CLON	138.4 ± 5.9^b	115.3 ± 1.4^a	106.5 ± 4.2^a
ST-91	197.1 ± 5.7^b	145.5 ± 5.0^b	126.5 ± 4.0^b
HR (beats/min)			
PLA	81.9 ± 4.1^a	82.6 ± 5.6^a	75.4 ± 3.2^a
DIAZ	104.5 ± 20.0^a	69.7 ± 6.2^a	63.1 ± 3.8^a
CLON	62.5 ± 7.6^a	64.8 ± 5.7^b	60.9 ± 4.9^a
ST-91	119.6 ± 31.1^a	50.6 ± 3.2^a	63.1 ± 1.4^a
PCV (%)			
PLA	29.4 ± 0.5^a	29.2 ± 1.1^a	28.6 ± 0.9^a
DIAZ	34.4 ± 0.4^a	28.6 ± 0.6^a	28.4 ± 0.9^a
CLON	35.4 ± 1.7^b	26.6 ± 1.2^a	25.8 ± 1.2^a
ST-91	43.0 ± 1.8^b	43.4 ± 1.9^b	39.2 ± 2.7^b

*PaO_2: partial pressure of oxygen in arterial blood; RR: respiratory rate; ΔPpl: maximum change in transpulmonary pressure; HR: heart rate; MAP: mean arterial pressure. Treatments: PLA: placebo; DIAZ: diazepam; CLON: clonidine ($n = 5$ for each treatment). Similar letters denote no significant difference between treatments ($P \leqslant 0.05$). (Least significance difference with Bonferroni's correction).

hypoxaemia differed (Fig. 2). Clonidine and ST-91 produced long lasting and severe hypoxaemia with mean PaO_2 levels of ≈ 40 mm Hg (5.3 kPa) and 50 mm Hg (6.6 kPa), respectively. The maximum decrease in PaO_2 was seen 10 min after drug administration; however, the values remained significantly lower than placebo levels throughout the whole period of study. Although there was a trend for clonidine to produce a greater degree of hypoxaemia, there was no significant difference between the degree of hypoxaemia produced by clonidine and ST-91 at any time interval (Table 1). The diazepam treated animals also showed a significant drop in PaO_2 levels by 2 min after drug administration; but by 10 min, PaO_2 levels were improving and at 15 min the values did not differ from placebo treated animals. The increase in alveolar-to-arterial oxygen gradient ($P(A\text{-}a)O_2$) after treatment with diazepam, clonidine or

ST-91 was essentially a mirror image of the decrease in PaO_2 (Fig. 2).

None of the drugs increased $PaCO_2$ levels when compared to saline treatment and the acid base variables did not show any significant change. A significant increase was recorded in the packed cell volume (PCV) of the ST-91 treated group throughout the study, with an increase at 5 and 10 min after clonidine administration (Fig. 3).

Cardiovascular variables

The initial heart rate (HR) was quite variable following administration of the three drugs, with ST-91 and diazepam tending to increase HR, and clonidine to decrease it (Fig. 3). When compared to the saline treated placebo group, all drug treated animals showed a significant decrease in HR at 45 min after drug administration. In addition, a significant decrease in HR was also noticed 30 min after ST-91 administration. Various changes in the rhythm and altered ECG wave forms were noticed in ST-91 treated animals. This included sinus arrhythmia, premature ventricular contractions, inverted and biphasic T waves and ST elevation.

Within 2 min of administration, all drugs caused a significant increase in mean arterial pressure (MAP) (Fig. 3). Compared to the placebo treated group, MAP remained increased up to 5 and 60 min after clonidine and ST-91 treatment, respectively.

When the responses of the three drugs were compared at selected time periods (Table 1) it was evident that clonidine and ST-91 affected PaO_2 in a similar manner. However, the response differed between the different drugs at some time periods for some of the other variables.

DISCUSSION

It is evident that a significant decrease in PaO_2 levels occurred with all three drugs; however, the fact that hypoxaemia was observed following ST-91 administration strongly suggests that the peripheral α_2 adrenoceptors are capable of inducing hypoxaemia, independent of a sedative response. On the other hand, the onset of hypoxaemia following administration of the non-α_2 agonist sedative, diazepam, suggests that central effects such as sedation and muscle relaxation can also play a complimentary role in bringing about hypoxaemia. The hypoxaemia caused by diazepam, however, was shorter in duration and was much less profound than that caused by clonidine and ST–91.

The overall respiratory and gas exchange response to the central and peripheral α_2 agonist clonidine was remarkably similar to that observed earlier with sedative doses of xylazine, romifidine, detomidine and medetomidine (Celly *et al.*, 1997), both from a quantitative and qualitative viewpoint. This response consists of tachypnoea, a large and sustained increase in ΔPpl, and severe hypoxaemia characterized by an increase in $P(A\text{-}a)O_2$ without hypoventilation. The degree of hypoxaemia produced by 15 µg/kg clonidine in the present study (i.e. $PaO_2 < 40$ mm Hg or 5.3 kPa) was very similar to that observed previously by Eisenach (1988) using a similar dose. Surprisingly, Eisenach
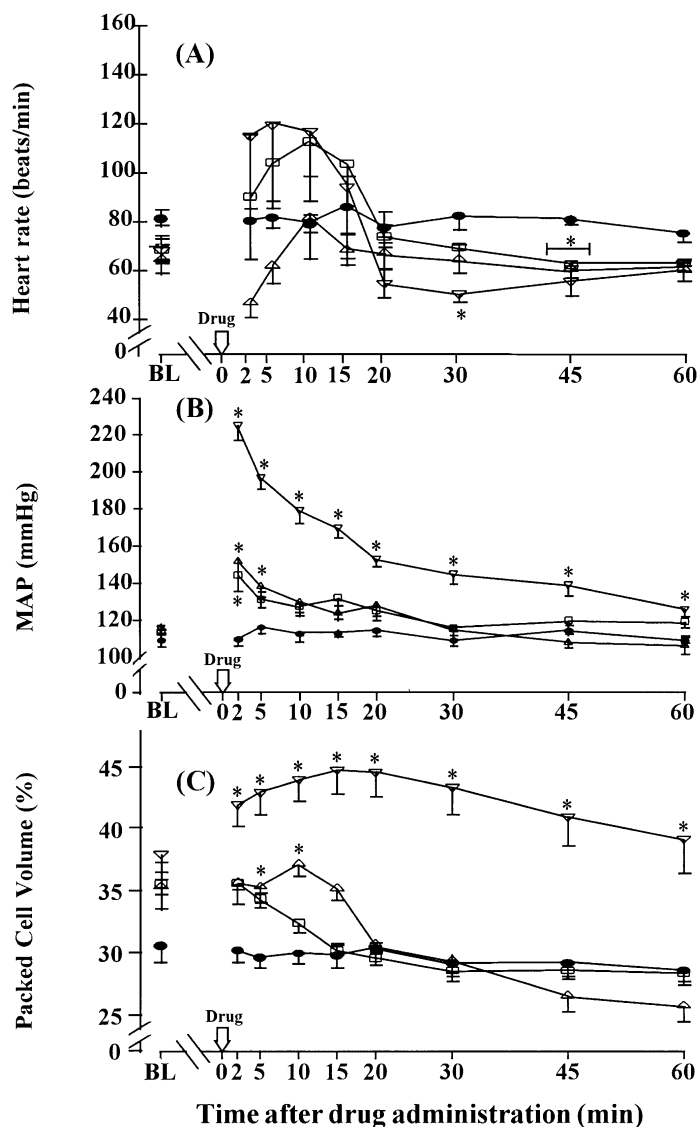
Fig. 3. Comparative changes in (A) heart rate (B) mean arterial pressure (MAP) and (C) packed cell volume (PCV), after administration of different treatments. Baseline (BL) values and response over 60 min are shown for diazepam (□, 0.4 mg/kg), clonidine (△, 15 µg/kg) and ST-91 (▽, 30 µg/kg) and placebo (●). Significant differences ($P \leqslant 0.05$) between different treatments and placebo are shown (*), as well as where all three agents differ from the placebo treatment (⊢—*—⊣). The statistical significance was established by Least significance difference test with Bonferroni's correction.

reported that none of his sheep appeared to experience 'overt respiratory distress' during the period of hypoxaemia after clonidine, a finding markedly different from the present study. He did not report respiratory rates and did not measure ΔPpl.

The respiratory and gas exchange response to ST-91 was directionally similar to the effect on respiratory rate, PaO_2, $P(A\text{-}a)O_2$ and ΔPpl, although the magnitude of change was less. Unlike clonidine, ST-91 tended to increase $PaCO_2$ levels for 20 min. There are a number of reasons for the diminished hypoxaemic response. It is possible that the central α_2 adrenoceptor activation and resultant sedative effects of clonidine added to respiratory distress; alternatively, it is possible that ST-91 is stimulating different subtypes of α_2 adrenoceptors (Takano & Yaksh, 1991; Yaksh *et al.*, 1995). It is also possible that the 15 µg/kg clonidine and 30 µg/kg ST-91 were not equivalent doses relative to their resultant activation of peripheral α_2 adrenoceptors. As ST-91 does not produce sedation, it was impossible to standardize doses on the basis of sedation. While Eisenach (1988) observed that ST-91 was a less potent hypoxaemic agent than clonidine in sheep (on a mg/kg

basis), he reported that the slopes of the hypoxaemic dose–response curves for the two drugs did not differ.

Diazepam administration was also accompanied by hypoxaemia lasting for 10–15 min. A significant decrease in PaO_2 levels following i.v. administration of diazepam has been reported previously in sheep (Wood & Harding, 1989). In the study by Wood and Harding, PaO_2 values decreased from a baseline value of 118.4 mm Hg (15.7 kPa) to 107.1 mm Hg (14.2 kPa), compared to the decrease in our experiment from 88.7 mm Hg (11.8 kPa) to 62.9 mm Hg (8.4 kPa). Based on the results of the present study, hypoventilation can be considered as a minor contributing factor to diazepam induced hypoxaemia, in that $PaCO_2$ levels tended to be higher than placebo (and pretreatment) values up to 15 min after diazepam administration. However, the peak mean $PaCO_2$ levels were only 42.1 mm Hg (6.5 kPa) at 2 min.

An increase in $P(A\text{-}a)O_2$ was observed for 10 min after diazepam administration. This measurement effectively removes the hypoventilation component for purposes of comparison, and the elevation in $P(A\text{-}a)O_2$ strongly suggests that there was an increase in pulmonary venous admixture after diazepam admin-

istration. An increase in pulmonary venous admixture can theoretically occur because of an increase in the scatter of ventilation/perfusion ratios within regional areas of the lung, or it might be due to an increase in right-to-left pulmonary shunt flow or a fall in cardiac output and the oxygen tension in mixed venous (pulmonary artery) blood (Benumof, 1994; McDonell, 1996). In other species, diazepam produces minimal cardiovascular effects with no fall in cardiac output (Muir *et al.*, 1982; Haskins *et al.*, 1986). In the present study diazepam treatment did not lower blood pressure or HR. It is most likely that the increase in P(A-a)O$_2$ is due to the sedation and muscle relaxation properties of diazepam, with resultant alterations in chest wall configuration and perhaps a decrease in functional residual capacity (FRC), leading to an increase in the scatter of ventilation/perfusion ratios in the lung. The relatively small increase in ΔPpl after diazepam (from 6.9 to a peak value of 14.7 cm H$_2$0 at 2 min and lasting only 10 min) was not associated with visible respiratory distress in the sheep, in contrast to the effect after clonidine or ST–91. While the difference in the duration of hypoxaemia with diazepam might be due to a more rapid elimination of this drug than occurred with clonidine, this is not very likely. The elimination $t_{0.5}$ of diazepam is 3.2–9 h in dogs (Frey & Löscher, 1985), however, the clinical sedation lasted for 30 min for each drug.

The marked and sustained increase in ΔPpl after treatment was even greater than observed in our earlier experiment with xylazine, romifidine, detomidine and medetomidine (Celly *et al.*, 1997), while the ST-91 response was similar in magnitude. This increase in ΔPpl is strongly suggestive of a pulmonary parenchymal origin for the increase in P(A-a)O$_2$ and decrease in PaO$_2$ in the clonidine and ST-91 treated sheep. An increase in ΔPpl is generally associated with an alteration of pulmonary mechanics (Tesarowski *et al.*, 1996), but there is no way of determining whether there was a decrease in lung compliance, an increase in pulmonary resistance, or both. In sheep, anaesthetized with a ketamine infusion, 15 μg/kg clonidine significantly increased the ratio of dead space ventilation to total ventilation and greatly increased intrapulmonary shunt flow (from 11 ± 4% to 72 ± 10% of total flow) (Eisenach, 1988). It appears therefore that there was an intrapulmonary origin to the clonidine-induced hypoxaemia, as speculated for the other α$_2$ agonists (Celly *et al.*, 1997). While it is possible that an alteration of chest wall shape and function occurs, perhaps with a decrease in FRC, the contribution of this component to the hypoxaemia must be minimal, as ST-91 produces the hypoxaemia without sedation. In support of this hypothesis, Nolan *et al.* (1986) and Papazoglou *et al.* (1994) observed an increase in the inflation pressure following i.v. administration of xylazine in anaesthetized sheep during intermittent positive pressure ventilation (IPPV), and sub-sedative doses of xylazine and detomidine still produce hypoxaemia (Waterman *et al.*, 1987).

The hypoxaemic response to the peripheral α$_2$ agonist ST-91 confirms the earlier work of Eisenach (1988), and provides convincing evidence that neither central sedation, nor central α$_2$ adrenoceptor activation is necessary to produce α$_2$ agonist-induced hypoxaemia. Eisenach speculated that the peripheral α$_2$ adrenoceptor activation by ST-91 (and clonidine) was associated with platelet aggregation. No morphological studies were reported to support his hypothesis (Eisenach, 1988). We also did not find any morphological evidence of platelet aggregation following xylazine or ST-91 treatment in conscious sheep (Celly, 1996). In the present study, ST-91 increased MAP from the pretreatment value of 116 mm Hg to 225 mm Hg within 2 min of administration. Such an acute response has also been associated with a decrease in PaO$_2$ levels secondary to left ventricular failure and pulmonary oedema (Eisenach, 1988). To confirm or refute this possibility, measurements of left atrial or pulmonary artery wedge pressure are required.

The common response following i.v. administration of sedative α$_2$ agonists includes an initial transient pressor response mediated by α$_1$ and α$_2$ adrenoceptor subtypes at post synaptic sites in vascular smooth muscle. This is followed by hypotension and bradycardia caused via stimulation of central α$_2$ adrenoceptors (Timmermans *et al.*, 1983). This explains the transient hypertensive response seen up to 10 min following clonidine administration, and the similar response observed earlier with romifidine and detomidine (Celly *et al.*, 1997). On the other hand ST-91, which can not cross the blood brain barrier (Scriabine *et al.*, 1977) and stimulate peripheral α$_2$ adrenoceptors, showed a long lasting hypertensive response. This increase in MAP has previously been reported following ST-91 administration in rats (Scriabine *et al.*, 1977) and sheep (Eisenach, 1988). In contrast to the α$_2$ agonists, i.v. administered diazepam typically produces a decrease in systemic vascular resistance, blood pressure, venous return, cardiac contractility and cardiac output (Jones *et al.*, 1979). Interestingly, we observed a transient, but significant, hypertension recorded at 2 min after diazepam administration.

Clonidine treatment did not significantly alter HR, as observed earlier with xylazine (Doherty *et al.*, 1986; Celly *et al.*, 1997). This is in contrast to the situation in other species where sedative doses of xylazine and other α$_2$ agonists usually produce bradycardia (Klide *et al.*, 1975; Doherty *et al.*, 1987; Wagner *et al.*, 1991; Pettifer & Dyson, 1993). In the present study, ST-91 increased HR for 15 min after administration, although the response was quite variable and was not significant. On the other hand, Eisenach (1988) observed significant bradycardia following the same dose of ST-91 in sheep. Given the marked increase in MAP and an intact vagal response, it is surprising that the sheep in our study did not show bradycardia. The HR and MAP response to diazepam was similar to the response seen in calves receiving 0.4 mg/kg i.v. (Mirakhur *et al.*, 1984).

In conclusion, the α$_2$ agonist-induced hypoxaemia in sheep appears to be mediated by peripheral α$_2$ adrenoceptors. The central effects of these drugs such as sedation and muscle relaxation may contribute to hypoxaemia, but they are much less important than the peripheral actions. Further studies are needed to differentiate the mechanisms underlying the hypoxaemia caused by the α$_2$ agonists.

ACKNOWLEDGMENTS

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