Preliminary investigation into the ventilatory effects of midazolam in isoflurane-anaesthetised goats

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The ventilatory effects of intravenous midazolam (MDZ) were evaluated in isoflurane-anaesthetised goats. Eight female goats aged 2–3 years were fasted from food and water for 12 h. Anaesthesia was then induced using a face mask with isoflurane in oxygen, whilst the trachea was intubated with a cuffed tracheal tube and anaesthesia maintained with isoflurane at 1.5% end-tidal concentration. Ventilation was spontaneous. The goats were treated with either a saline placebo (PLC) or MDZ intravenously at 0.2 mg/kg. Analysis of variance for repeated measures was used for the analysis of data. Significance was taken at the 0.05 level. Differences between treatments were not statistically significant ($p > 0.05$) for tidal volume, ventilation rate, tidal volume/kg (V_T/kg) and end-tidal carbon dioxide partial pressure. Within treatments, V_T and V_T/kg differed 5 min after MDZ administration; this was statistically significant ($p < 0.05$). The occurrence of apnoea in the MDZ-treated goats was statistically significant ($p = 0.04$) compared with the PLC treated goats. Intravenous MDZ at 0.2 mg/kg administered to isoflurane-anaesthetised goats may result in transient apnoea and a mild decrease in V_T and V_T/kg.

Introduction

Until 2009, acepromazine (Aceprom, Bayer AH, Isando, South Africa) was the only tranquiliser registered in South Africa for use in sheep,[1] whilst, at present, a generic acepromazine (Neurotranq, Virbac, Halfway House, South Africa) is registered in this country for cattle and horses, but not for sheep or goats. With acepromazine sedation, arousal is accomplished easily[2] and is therefore not reliable for restraint during surgical procedures performed under local anaesthesia. Xylazine induces dose-dependent sedation in sheep and goats[3]; yet, in South Africa, xylazine is only registered for use in cattle[1] and its use in sheep and goats may result in adverse cardiopulmonary effects such as hypoxia, pulmonary oedema and pulmonary alveolar haemorrhage.[4,5,6]

Midazolam (MDZ) is used commonly in humans for pre-anaesthetic medication and induction of anaesthesia.[7] Respiratory depression is a common adverse effect in humans and is associated with a decrease in tidal volume (V_T) and minute ventilation (V_E).[8] Apnoea may also occur during conscious sedation.[9] In dogs, apnoea occurs after premedication with MDZ and induction of anaesthesia with propofol.[10] The intravenous administration of MDZ to conscious goats results in a decrease in V_E and arterial oxygen tension.[10] Therefore, the pre-anaesthetic use of MDZ possibly may result in increased ventilatory depression during maintenance of anaesthesia with isoflurane. This investigation is a preliminary investigation into the ventilatory effects of MDZ in goats during isoflurane anaesthesia.

Materials and methods

A prospective laboratory anaesthesia goat model was used in a randomised two-period, placebo-controlled crossover study design. A washout period of two weeks was allowed between crossover treatments. Eight healthy, female goats aged 2–3 years, with a mean body mass of 47.3 kg ± 9.6 kg were used in the investigation. The goats were treated either with MDZ or a saline placebo (PLC).

After a 12 h pre-anaesthetic fast from food and water, anaesthesia was induced and maintained with isoflurane in oxygen (Forane, Abbott, Weltevreden Park, South Africa). During induction, a facemask was applied until the laryngeal reflex was depressed to allow tracheal intubation with a cuffed tracheal tube. Anaesthesia was maintained on a circle anaesthetic machine with carbon dioxide (CO_2) absorption. Isoflurane was delivered by an agent-specific vaporiser (Isotec, MkIII, Scientific Group, Randburg, South Africa), with the fresh gas flow rate set at 30 mL/kg/min for the first 15 min and thereafter reduced to 10 mL/kg/min. Ventilation was spontaneous and the vaporiser setting was adjusted to maintain the end-tidal isoflurane concentration at 1.5%. Monitoring was performed with a calibrated multifunction anaesthetic

monitor equipped with a sidestream spirometer using a single airway adapter (D-LITE; S/5 Anaesthesia Monitor, Datex-Ohmeda, Helsinki, Finland). During the investigation, the goats were maintained in sternal recumbency on a specially constructed table. The jugular vein was catheterised with an 18 G teflon catheter (Jelco, Johnson & Johnson, Tokai, South Africa) for drug and fluid administration. Treatment was administered after a 15 min stabilisation period and the observer was blinded. Either saline PLC or MDZ (Dormicum, Roche, Isando, South Africa) was administered intravenously at a dose of 0.2 mg/kg as a bolus over 30 s (Time period, T0). Airway gasses were sampled continuously from the airway adaptor and variables updated breath by breath. The mean value from five consecutive ventilation cycles was used for each expired tidal volume (V_T) calculation. Measurement of variables was made at baseline (T-5) and at 5 min intervals after treatment for a period of 15 min (T5 to T15). The following variables were measured: duration of apnoea (seconds), ventilation rate (F, breaths per min), V_T (mL), end-tidal CO_2 partial pressure ($ETCO_2$, kPa) and end-tidal isoflurane concentration (ETiso, %). Tidal volume/kg body weight (V_T/kg, mL/kg) was also calculated.

Data analysis

Data were reported as the mean ± s.d., whilst Mauchly's test of sphericity was used to test for normality of data distribution. When data were not normally distributed, the Greenhouse-Geisser adjustment for degrees of freedom was applied. Levene's test for equality of error variances was applied for repeated measures. A general linear model for repeated measures procedure was used for analysis of variance for between subject factors treatment and crossover period. A chi-square test was used to evaluate the incidence of apnoea after treatment administration. Significance was accepted at the 95% confidence level. Data analysis was performed on a personal computer using the SPSS 19 statistical software program (Olrac SPS, Cape Town, South Africa).

Ethical considerations

The Animal Use and Care Committee and the Research Committee of the Faculty of Veterinary Science at the University of Pretoria approved the protocol (Project No. 36.5.442) for this investigation.

Potential benefits and hazards

Midazolam may improve the quality of sedation in goats. The administration of anaesthesia exposes goats to potential risks such as the aspiration of rumen contents. Measures to reduce the risk of aspiration were fasting from food and water and induction was performed in sternal recumbency until tracheal intubation was performed.

Results

Data distribution was normal and error variances were equal between treatment groups ($p > 0.05$). In the MDZ group, the incidence of apnoea was statistically significant ($p = 0.04$) compared with the PLC-treated goats. In four of the eight goats, apnoea occurred within 90 s of MDZ intravenous administration, with the duration of 30 s, 70 s, 80 s and 120 s, respectively. No apnoea was observed in the PLC group. The mean ± s.d. values for PLC and MDZ for F were: 12.1 ± 2.9 breaths per min and 12.2 ± 3.7 breaths per min, respectively. Other results included: V_T = 279.0 mL ± 45.0 mL and 249.0 mL ± 46.0 mL, V_T/kg = 6.3 mL ± 0.6 mL and 5.6 mL ± 0.6 mL and $ETCO_2$ = 9.36 kPa ± 1.09 kPa and 9.14 kPa ± 1.4 kPa, for the PLC and MDZ groups respectively. Differences between treatments ($p = 0.52$) and between crossover periods ($p = 0.56$) were not statistically significant.

For within treatment comparison of changes over time, the changes in the individual variables for PLC were not statistically significant: V_T ($p = 0.85$), F ($p = 0.2$), V_T/kg ($p = 0.91$) and $ETCO_2$ ($p = 0.08$). For MDZ, individual changes over time were also not statistically significant: V_T ($p = 0.07$), F ($p = 0.08$), V_T/kg ($p = 0.09$) and $ETCO_2$ ($p = 0.7$). For PLC, the contrasts from T5 to T15 with T-5 were not statistically significant ($p < 0.05$) for any of the variables. For MDZ, the contrasts to T-5 were statistically significant for V_T ($p = 0.01$) and V_T/kg ($p = 0.008$) at T5. None of the other time periods were statistically significant from T-5 (Table 1).

Discussion

Apnoea was a statistically significant event that occurred after MDZ administration. Return of spontaneous ventilation was between 30 s and 120 s and statistically significant changes for V_T and V_T/kg were observed after 5 min; this was

TABLE 1: Temporal changes in ventilation variables after midazolam or placebo treatment in isoflurane-anaesthetised goats.

Variables	Rx	T-5	T5	T10	T15
F	PLC	11.40 ± 3.50	13.30 ± 3.80	11.80 ± 2.50	11.30 ± 2.10
V_T (mL)	PLC	294.00 ± 61.00	283.00 ± 54.00	277.00 ± 43.00	277.00 ± 43.00
V_T/kg (mL)	PLC	6.40 ± 1.80	6.30 ± 1.60	6.10 ± 2.00	6.10 ± 2.00
$ETCO_2$ (kPa)	PLC	8.13 ± 2.10	9.56 ± 1.44	9.24 ± 0.94	9.30 ± 0.94
ETiso (%)	PLC	1.50 ± 0.00	1.50 ± 0.06	1.50 ± 0.04	1.50 ± 0.05
F	MDZ	14.50 ± 3.90	13.30 ± 4.70	12.00 ± 3.60	11.30 ± 2.60
V_T (mL)	MDZ	278.00 ± 46.00	243.00 ± 52.00*	252.00 ± 45.00	252.00 ± 45.00
V_T/kg (mL)	MDZ	6.40 ± 1.90	5.10 ± 1.80*	5.30 ± 1.60	5.50 ± 1.70
$ETCO_2$ (kPa)	MDZ	9.12 ± 1.06	9.46 ± 1.14	8.83 ± 1.73	9.12 ± 1.37
ETiso (%)	MDZ	1.50 ± 0.00	1.50 ± 0.04	1.50 ± 0.05	1.50 ± 0.04

Data reported as the mean ± standard deviation.
Rx, treatment; Tn, 5 min time interval; PLC, placebo; MDZ, midazolam; F, ventilation rate; V_T, tidal volume; V_T/kg, tidal volume/kg; $ETCO_2$, end-tidal carbon dioxide partial pressure; ETiso, end-tidal isoflurane concentration.
*, Statistically significant different ($p < 0.05$) from T-5.

associated with decreased values compared with baseline (T-5, Table 1). Variability in V_T values as a result of differences in bodyweight was eliminated with the calculation of V_T/kg.

End-tidal CO_2 was affected minimally at T5, which could be the result of the transient effect of MDZ on ventilation. Values reported for the ventilation rate and tidal volume in goats (20–40 breaths per min and 7 mL/kg – 8 mL/kg)[11] are higher compared with the values observed during isoflurane anaesthesia in this investigation (13.3 ± 3.8 breaths per min and 6.3 mL/kg ± 1.6 mL/kg). Hypercapnoea occurred in both treatments, which was the result of the isoflurane anaesthesia, and the administration of MDZ did not increase ventilatory depression associated with increases in $ETCO_2$. Arterial blood gas analysis was unfortunately not performed because of financial limitations.

A comparison of differences between treatments was not statistically significant and this could possibly be ascribed to the transient effect of MDZ on ventilation. It is conventional to take the level of significance at 0.05, but if statistical significance was taken at 0.1, the differences between treatments for V_T ($p = 0.07$) would have been significant.

Conclusion

In humans, MDZ decreases the ventilatory response to CO_2,[9,12] decreases tidal volume, increases ventilation rate with minute ventilation unaltered[13] and is similar to the observation in this investigation. Isoflurane is a potent volatile inhalation anaesthetic agent with respiratory depressant effects in humans[14] and animals[15,16]. With the administration of MDZ to isoflurane-anaesthetised goats, the possible additive or synergistic interaction with isoflurane on ventilation should be considered. In a similar manner to isoflurane, the ventilatory depressant effects of midazolam are mediated centrally, where it acts on gamma amino benzoic acid (GABA) receptors and potentiates the action of GABA, a major inhibitory neurotransmitter in the central nervous system.[17]

The intravenous administration of MDZ at 0.2 mg/kg during 1.5% end-tidal isoflurane concentration anaesthesia in goats resulted in a transient apnoea and a mild decrease in V_T and V_T/kg. These findings suggest that midazolam is suitable for perioperative sedation in goats and warrant further detailed investigations into its cardiopulmonary effects.

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Competing interests

The authors declare that they have no financial or personal relationship(s) which may have inappropriately influenced them in writing this paper.

Authors' contributions

G.F.S. (University of Pretoria) was project leader responsible for experimental and project design, as well as performing the experiments. L.B. (University of Pretoria) assisted in preparing the blinded treatments and the collection of data.

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