

Some cardiopulmonary effects of midazolam premedication in clenbuterol-treated bitches during surgical endoscopic examination of the uterus and ovariohysterectomy

G F Stegmann^a and L Bester^a

ABSTRACT

Midazolam was administered intravenously to 8 bitches in a randomised, placebo-controlled clinical trial before propofol induction of surgical anaesthesia. Anaesthesia was maintained with isoflurane-in-oxygen during surgical endoscopic examination of the uterus and ovariohysterectomy. Clenbuterol was administered at the start of surgery to improve uterine muscle relaxation, and to facilitate endoscopic examination of the uterus. Ventilation was controlled. Induction of anaesthesia with propofol to obtain loss of the pedal reflex resulted in a statistically significant ($P < 0.05$) decrease in minute volume and arterial oxygen partial pressure in the midazolam group. Apnoea also occurred in 50 % of dogs in the midazolam group. The dose for propofol in the midazolam group was 7.4 mg/kg compared to 9.5 mg/kg in the control. Minute volume was significantly ($P < 0.05$) higher in both groups during isoflurane maintenance, compared to the value after incremental propofol to obtain loss of the pedal reflex. Propofol induction resulted in a 25–26 % reduction in the mean arterial blood pressure in both groups, and the administration of clenbuterol at the start of surgery resulted in a transient, but statistically significant ($P < 0.05$), decrease in mean arterial blood pressure in the midazolam group during isoflurane anaesthesia. It is concluded that intravenous midazolam premedication did not adversely affect cardiovascular function during propofol induction, but intra-operative clenbuterol during isoflurane maintenance of anaesthesia may result in transient hypotension. Midazolam premedication may increase adverse respiratory effects when administered before propofol induction of anaesthesia.

Key words: anaesthesia, canine, cardiopulmonary, clenbuterol, midazolam, propofol.

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INTRODUCTION

It has been suggested that the intra-operative administration of clenbuterol may facilitate the endoscopic examination of the canine uterus for diagnostic purposes. Clenbuterol is a selective β_2 -adrenergic agonist that is administered to induce bronchial dilation and myometrial relaxation. Possible adverse effects that may occur are systemic hypotension and cardiac arrhythmias when used in conjunction with inhalation anaesthetic agents, and in particular in animals with pre-existing cardiac disease¹³. The use of this agent during anaesthesia is not recommended by the manufacturer, and its use during anaesthesia is listed as contra-indicated.

Midazolam minimally affects arterial blood pressure, and is recommended for animals with compromised cardiovascular function,⁹ but may decrease minute ventilation in humans² and animals¹⁷. Isoflurane is suitable for animals with compromised cardiovascular function¹⁰, but results in a decrease in peripheral vascular resistance⁶, similar to midazolam³ and propofol¹⁴. The combined use of midazolam and isoflurane may therefore decrease systemic arterial blood pressure and possibly also minute ventilation. Investigations in anaesthetised horses indicated possible adverse cardiopulmonary effects such as hypoxaemia when clenbuterol was administered intravenously⁵. The purpose of the investigation was to examine the effects of midazolam premedication on some cardiopulmonary variables after: (1) propofol induction at 2 different dose rates, and (2)

intravenous clenbuterol in isoflurane-anaesthetised bitches during endoscopic examination of the uterus and ovariohysterectomy.

MATERIALS AND METHODS

Eight healthy German shepherd bitches with a mean body mass of 26.9 kg, ranging between 25 and 31 kg, and 9–31 months old, were scheduled for endoscopic examination of the uterus, and ovariohysterectomy. The animals were randomly allocated to 2 groups of 4 each. A 20 G catheter (Jelco, Johnson & Johnson) was introduced percutaneously into the dorsal pedal artery for direct arterial blood pressure measurement, and collection of arterial blood for blood-gas analysis. A similar catheter was introduced into the cephalic vein for the administration of propofol and Ringer Lactate. The latter was administered at a rate of 10 ml/kg/min during surgery. Arterial blood samples were anaerobically collected in 3-ml heparinised plastic syringes, stored in iced water, and analysed within 2 h of collection with a blood-gas analyser (ABL300 Radiometer). The samples were corrected for body temperature. Blood samples were collected before induction, after incremental propofol, and at the end of the endoscopic examination.

Group A was premedicated 2 min before induction with intravenous midazolam (Dormicum, Roche) at a dose of 0.2 mg/kg, and Group B treated with saline placebo before induction. The observer was blinded to the treatment administered. Both groups were induced with intravenous propofol (Diprivan, Zeneca) at 4 mg/kg, administered as a bolus over 60 sec. The trachea was intubated with a cuffed silicon endotracheal tube. Incremental propofol was added at a dose of 1 mg/kg until loss of the pedal reflex was achieved. Anaesthesia was maintained with a circle anaesthetic machine with carbon dioxide absorption, and an out-of-circuit precision isoflurane vaporiser (Fortec MK III, Cyprane). Fresh gas flow rate was set at 30 ml/kg/min after induction of anaesthesia, and decreased

^aDepartment of Companion Animal Surgery, Faculty of Veterinary Science, University of Pretoria, Private Bag X04, Onderstepoort, 0110 South Africa.

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Table 1: Mean (\pm SD) perioperative cardiopulmonary and arterial blood-gas variables in dogs premedicated with midazolam, induced with propofol, and maintained with isoflurane.

Variable	Rx ¹	Preop ²	Prop1 ³	Prop2 ⁴	Iso ⁵
HR (beats/min) ⁶	Mdz	105 (31)	118 (28)	118 (20.5)	125 (18)
	Plc	121 (11)	134 (11)	138 (13)	128 (16.4)
MAP (kPa) ⁷	Mdz	14.2 (2.0)	11.0 (2.8)	11.2 (4.7)	10.2 (3.2)
	Plc	16.8 (5.6)	12.7 (2.0)	16.4 (4.4)	9.9 (3.4)
V _E (l) ⁸	Mdz	–	7.4 (1.8)	1.7 (2.0)*	7.5 (1.9)
	Plc	–	7.7 (2.5)	7.9 (1.8)	8.4 (2.3)
V _T (ml) ⁹	Mdz	–	205 (63)	120 (138)	310 (73)
	Plc	–	242 (94)	252 (24)	297 (79)
F (breaths/min) ¹⁰	Mdz	21 (13)	43 (16)	9 (10)	23 (4.7)
	Plc	51 (12)	28 (13)	31 (2)	27 (4.5)
ETCO ₂ (%) ¹¹	Mdz	–	5.5 (0.4)	2.6 (3.0)	6.1 (0.6)
	Plc	–	5.4 (0.6)	6.1 (0.1)	6.5 (0.8)
pH	Mdz	7.35 (0.03)	–	7.38 (0.03)	7.35 (0.01)
	Plc	7.29 (0.01)	–	7.36 (0.03)	7.30 (0.01)
PaO ₂ (kPa) ¹²	Mdz	11.1 (0.7)	–	5.2 (1.8)*	60.5 (0.5)
	Plc	9.2 (0.4)	–	6.6 (0.9)	55.5 (0.9)
PaCO ₂ (kPa) ¹³	Mdz	4.6 (0.2)	–	5.4 (0.6)	6.4 (0.4)
	Plc	4.4 (0.1)	–	4.9 (0.4)	6.0 (1.2)
HCO ₃ (mmol/l) ¹⁴	Mdz	20.1 (1.8)	–	21.3 (1.0)	19.0 (1.6)
	Plc	18.1 (0.2)	–	19.5 (1.1)	19.9 (1.6)
SBE (mmol/l) ¹⁵	Mdz	–3.9 (2.0)	–	–3.3 (1.1)	–7.4 (2.3)
	Plc	–6.3 (0.1)	–	–5.2 (1.0)	–5.8 (0.7)
SAT (%) ¹⁶	Mdz ¹⁷	94.7 (0.7)	–	59.3 (25)*	99.9 (0.1)
	Plc ¹⁸	91.6 (1.0)	–	79.7 (10.2)	99.9 (0.0)

1 = treatment group; 2 = preoperative; 3 = propofol (4 mg/kg); 4 = propofol dose at loss of pedal reflex; 5 = isoflurane; 6 = heart rate; 7 = mean arterial blood pressure; 8 = minute volume; 9 = tidal volume; 10 = ventilation rate; 11 = end-tidal carbon dioxide concentration; 12 = arterial partial pressure of oxygen; 13 = arterial partial pressure of carbon dioxide; 14 = bicarbonate concentration; 15 = standard base excess; 16 = oxyhaemoglobin saturation; 17 = midazolam; 18 = placebo.

*Statistically significant change ($P < 0.05$).

to 10 ml/kg/min when the pedal reflex disappeared. Ventilation was controlled after induction of anaesthesia with a mechanical ventilator (Penlon AV800 Intermed) with an inspiratory pressure of 20 cmH₂O, and an inspiratory:expiratory time ratio of 1:2. The ventilation rate was set at a rate of 20–30 breaths/min to maintain an end-tidal carbon dioxide concentration (ETCO₂) between 5% and 6%. The inspired isoflurane (Forane, Abbott) concentration was adjusted to the minimum concentration required to maintain absence of the pedal reflex during surgery. At the start of the abdominal skin incision, clenbuterol hydrochloride (Planipart, Janssen) was administered intravenously at a dose of 1.2 µg/kg.

Multiparameter physiological monitors were used to measure the cardiopulmonary variables. The Cardiocap II (Datex) was used to monitor the electrocardiogram, with a 3-limb lead and disposable electrodes attached to the limbs. Arterial blood pressure was measured with a calibrated strain gauge pressure transducer connected to the pedal artery. The Capnomac Ultima (Datex) with side-stream spirometer was attached to the endotracheal tube to measure tidal volume, minute volume, ventilation rate and

ETCO₂ concentration. The cardiopulmonary variables were recorded at similar intervals to those between arterial blood collection during induction, and at 5 min intervals during inhalation maintenance of anaesthesia. The values were recorded on a standard anaesthetic monitoring sheet

Data analysis

Data are reported as mean (\pm SD). Two-way analysis of variance for repeated measures was used to analyse the data for treatment and time. When significant differences were found, the Tukey test was applied. Analysis of data was performed on a personal computer using SigmaStat (Jandel Scientific). Significance was accepted at $P < 0.05$. The investigation was approved by the Ethics and Research Committees of the University of Pretoria.

RESULTS

The intra-operative cardiopulmonary and blood-gas variables are reported in Table 1 as the mean and standard deviation (\pm SD). A non-significant decrease in the mean arterial blood pressure occurred in both groups after induction with propofol. In the midazolam group, the

pressure was unchanged after the incremental dose of propofol; however, in the placebo group, the mean arterial pressure increased from 12.7 (2.0) to 16.4 (4.4) kPa during the same period (Fig. 1). The mean incremental dose for propofol to obtain loss of the pedal reflex was 3.4 and 5.5 mg/kg for the midazolam and control group respectively¹⁸. The administration of clenbuterol resulted in a decrease in the mean arterial pressure from 11.8 (2.1) to 8.7 (0.5) kPa, and 10.3 (1.3) to 7.7 (0.7) kPa respectively in the midazolam (26) and placebo (25%) groups (Fig. 1). An increase in blood pressure was observed in both groups within 10 min of clenbuterol administration. The heart rate increased after induction with propofol and during maintenance with isoflurane in both groups. No cardiac arrhythmias were observed after clenbuterol administration during maintenance of anaesthesia.

The mean minute volume decreased significantly ($P < 0.05$) from 7.4 (1.8) to 1.7 (2.0) l/min after incremental propofol administration to obtain loss of the pedal reflex in the midazolam group, but remained unaltered in the placebo group (Table 1). Apnoea occurred in 2 of the 4 animals in the midazolam group. With spontaneous ventilation at the start of

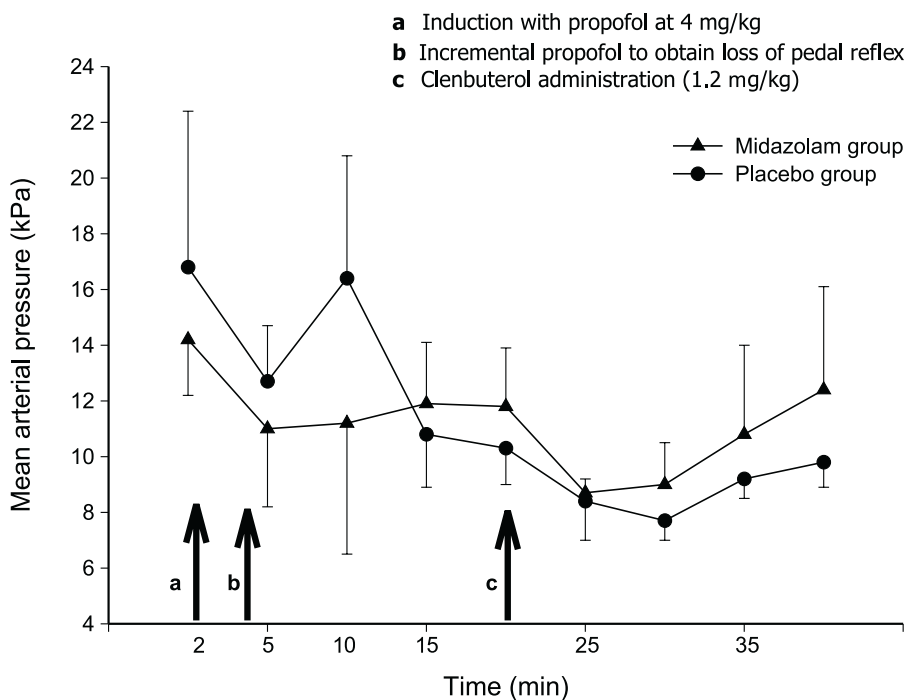


Fig 1: Mean (\pm SD) arterial blood pressure in dogs before and after propofol induction, and intravenous clenbuterol administration during isoflurane maintenance of anaesthesia for endoscopic examination and ovariohysterectomy.

abdominal suturing, minute volume increased significantly ($P < 0.05$) from 1.7 (2.0) and 7.9 (1.8) after the incremental propofol administration, to 14.2 (2.0) and 11.8 (1.1) l/min for the placebo and midazolam groups respectively. The minimum end-tidal isoflurane concentration required to maintain absence of the pedal reflex during surgery was 1.7 and 2.2 % for the midazolam and control groups respectively. The clinical effects observed during this study will be reported separately. The decrease in PaO_2 and arterial oxyhaemoglobin saturation were statistically significant ($P < 0.05$) in the midazolam group after induction of surgical anaesthesia (Table 1). In both groups, the PaCO_2 and ET-CO_2 increased after induction with propofol and during maintenance with isoflurane. A metabolic and respiratory acidosis were observed in both groups. The duration of anaesthesia was 80.3 (8.2) and 82.8 (10.6) min for the midazolam and control groups respectively.

DISCUSSION

The purpose of this investigation was to examine the effects of midazolam premedication on some cardio-pulmonary variables after propofol induction, and in clenbuterol-treated dogs during surgery and isoflurane maintenance of anaesthesia. Large variation in the variables of some parameters may have prevented statistically significant differences despite apparent large differences in mean values.

As the magnitude of the decrease in mean arterial blood pressure was the same in both groups (24 and 23 %) after induction with propofol at a dose of 4 mg/kg, it appeared that the blood pressure was minimally affected by midazolam. Minimal changes in blood pressure may occur after midazolam administration as result of peripheral vasodilation³. In addition, propofol decreases arterial blood pressure as result of venodilation⁸ and myocardial depression⁴. During this investigation, the blood pressure increased in the placebo group after incremental propofol, compared to the pressure that remained unaltered in the midazolam group. The increase in blood pressure was probably the result of endotracheal intubation, as the dogs were intubated before the incremental propofol administration. This may indicate that midazolam prevented the reflex sympathetic increase in blood pressure associated with endotracheal intubation¹⁸. However, the heart rate remained unaltered in both groups between the propofol administrations.

The decrease in the arterial blood pressure observed in this investigation after clenbuterol administration (26 %), was similar to the decrease observed in halothane-anaesthetised horses (28 %) treated with clenbuterol^{5,15}. In addition, isoflurane also causes peripheral vasodilation⁶, and could potentiate the hypotensive effects of midazolam and clenbuterol. Unfortunately, the design of this investigation did not allow comparison

with a control group not treated with clenbuterol. The decrease in blood pressure was of short duration, as an increase in pressure was observed in both groups within 10 min after clenbuterol administration (Fig. 1). The mean arterial blood pressure values from dogs premedicated with acepromazine, induced and maintained with propofol during deep anaesthesia¹⁶, were similar (11.2) compared to the midazolam group (11.0 kPa) in this investigation. As healthy animals were used in this investigation, it may be assumed that the homeostatic mechanisms were minimally affected. However, the administration of clenbuterol to anaesthetised and cardiovascularly compromised animals during clinical treatment may result in intra-operative hypotension, and can therefore not be recommended.

Clenbuterol was administered during this investigation to facilitate surgical endoscopic examination of the uterus for possible future use as a clinical diagnostic aid. This agent is a selective β_2 -adrenergic agonist that relaxes smooth muscle, and therefore results in systemic vasodilation¹³. It may also have minimal β_1 -adrenergic activity that can cause tachycardia and ventricular arrhythmias^{7,13}. Its administration during anaesthesia in horses^{5,7,12,15} has been reported previously, but not its intravenous administration during anaesthesia in dogs. Intra-operative duodenal administration in dogs resulted in a 15 % decrease in arterial blood pressure¹¹, and a decrease of 31 % in horses anaesthetised with intravenous agents⁵. In this investigation, it appeared that mean arterial blood pressure was only transiently decreased in midazolam-premedicated dogs after clenbuterol administration during isoflurane anaesthesia.

Midazolam in humans² and goats¹⁷ decreases ventilation. The decrease in minute volume after incremental propofol in the midazolam group was statistically significant ($P < 0.05$), and resulted in apnoea in 2 dogs. As the ventilatory variables were not measured before induction, minute volume after incremental propofol administration was compared with a quasi-equipotent isoflurane dose at the start of skin suturing. As the duration of anaesthesia was approximately 80 min in both groups, it can be assumed that the effects of propofol were negligible at this stage. The differences in minute ventilation for both groups were statistically significant ($P < 0.05$), and therefore probably the result of propofol administration. The total dose of propofol administered in the midazolam group was 7.4 mg/kg compared to

9.5 mg/kg in the control group. The ventilatory depression from midazolam was apparent from the significant decrease in minute ventilation (Table 1) despite a decrease in the propofol dose. Values obtained for the PaCO₂ and ETCO₂ concentrations remained within accepted physiological limits immediately after induction of anaesthesia, and were maintained at the same levels during maintenance of anaesthesia as result of positive-pressure ventilation. The hypoventilation and hypoxaemia observed in both treatment groups, and the apnoea that occurred in 50% (2 of 4) of dogs in the midazolam-premedicated group, were clinically significant. Apnoea from propofol has only been reported after a deliberate overdose in dogs¹⁶. Midazolam premedication may therefore increase ventilatory depression as evidenced by the apnoea, and the statistically significant ($P < 0.05$) decrease in the PaO₂ and oxyhaemoglobin saturation (Table 1). Hypoxaemia occurred after induction of anaesthesia as the PaO₂ decreased to 6.6 and 5.2 kPa for the placebo and midazolam groups respectively. Increased inspired oxygen concentration and increased minute ventilation from controlled ventilation improved the oxygen tension during inhalation maintenance of anaesthesia in both groups. Anaesthesia of dogs with propofol to a deep stable plane resulted in PaO₂ tensions of 8.8 kPa¹⁶, higher than the tensions recorded in this investigation (6.6 kPa). Oxyhaemoglobin saturation decreased to 88%,¹⁶ higher than the values obtained (59.3%) in this investigation. The PaCO₂ was less in this investigation (5.4 kPa) compared to the dogs (6.7 kPa)¹⁶. In horses anaesthetised with intravenous agents, hypoxaemia was potentiated by clenbuterol through increased pulmonary shunting⁵. The high arterial oxygen tension (60.5 kPa) and

oxyhaemoglobin saturation (99.9%) observed after positive-pressure ventilation with isoflurane-in-oxygen may indicate that pulmonary shunting was not of clinical significance in this investigation.

It is concluded that adverse effects such as hypoventilation and hypoxaemia may occur after induction of anaesthesia with propofol. In addition, midazolam premedication may result in apnoea after propofol administration to obtain surgical anaesthesia (loss of the pedal reflex). To avoid apnoea, it is recommended that the dose of propofol be reduced during the co-administration of agents that may depress ventilation such as midazolam and propofol. Clenbuterol administration during isoflurane maintenance of anaesthesia resulted in a transient decrease in arterial blood pressure, and midazolam premedication significantly influenced the decrease in arterial blood pressure.

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