

## Some clinical effects of midazolam premedication in propofol-induced and isoflurane-maintained anaesthesia in dogs during ovariohysterectomy

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### ABSTRACT

In a randomised, placebo-controlled clinical trial, anaesthesia was induced with propofol (4 mg/kg) after intravenous premedication with or without midazolam (0.1 mg/kg), in a group of 8 dogs scheduled for ovariohysterectomy. Midazolam administration induced acute behavioural changes, and increased reflex suppression after propofol induction. Compared to the control group, the dose required to obtain loss of the pedal reflex was significantly reduced by 37%, and the end-tidal isoflurane concentration during maintenance, reduced by 23 %.

**Key words:** anaesthesia, dogs, isoflurane, midazolam, premedication, propofol.

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### INTRODUCTION

The benzodiazepines are recommended for pre-anaesthetic medication in compromised animals owing to their benign cardiovascular effects<sup>4</sup>. In dogs and cats, midazolam does not induce a dose-dependent sedative-hypnotic effect as observed in humans<sup>15</sup> and goats<sup>19</sup>. The possibility exists that other recognised pharmacological effects such as an anaesthetic-sparing effect may not be as evident in dogs as in humans. Both midazolam and propofol act at the GABA<sub>A</sub> receptor site, and a synergistic interaction enhances their clinical effects when coadministered in man<sup>3,7</sup>. Clenbuterol was administered during this trial to facilitate endoscopic examination of the uterus before ovariohysterectomy. This agent may significantly influence cardiopulmonary function<sup>3,7</sup>, and transient changes in arterial blood pressure were observed during this investigation. The effects of clenbuterol on cardiopulmonary function during this investigation have been reported elsewhere<sup>20</sup>. The purpose of this paper was to report on the influence of midazolam premedication on the dose required for propofol induction and isoflurane maintenance of anaesthesia in dogs during surgery.

### MATERIALS AND METHODS

Eight German shepherd bitches with a body mass between 25 and 30 kg, and aged 9 to 31 months, scheduled for endoscopic examination of the uterus and ovariohysterectomy, were randomly allocated to 2 groups of 4 animals each. A 20 G catheter (Jelco, Johnson & Johnson) was introduced percutaneously into the cephalic vein for drug administration, and Ringer Lactate® (Sabax) was administered at a rate of 10 ml/kg/min during maintenance of anaesthesia. Group A was premedicated 2 minutes before induction with intravenous midazolam (Dormicum, Roche) at a dose of 0.2 mg/kg, and Group B (control) 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 depth of anaesthesia was judged subjectively according to a predetermined scale as outlined in Table 1, using eyeball rotation, palpebral and pedal reflexes. The trachea was intubated with a cuffed silicon endotracheal tube. Thereafter, propofol was injected in incremental doses of 1 mg/kg until the pedal reflex was absent. Anaesthesia was maintained with isoflurane-in-oxygen (Forane, Abbott) using 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 to 10 ml/kg/min when the pedal reflex disappeared. Ventilation was controlled after induction of anaesthesia with a mechanical ventilator (Penlon AV800 Intermed). Ventilation was set at an inspiratory pressure of 20 cmH<sub>2</sub>O, 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 (ET) carbon dioxide concentration between 5 and 6 %. The vaporiser was adjusted to the minimum isoflurane 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 for myometrial relaxation to facilitate endoscopic examination of the uterus.

The Cardiocap II (Datex) was used to monitor the electrocardiogram with a 3-lead and disposable electrodes attached to the limbs. Body temperature was measured with the probe introduced into the cervical oesophagus. The Capnomac Ultima (Datex) was attached to the endotracheal tube to measure the end-tidal isoflurane (ETiso) concentration (%).

### Data analysis

Data were reported as mean (±SD). Two-way analysis of variance (ANOVA) for repeated measures was used to analyse the data for treatment and time. When significant differences were found, the Tukey test was applied. The Students' *t*-test was used to test for differences in anaesthetic doses. Mann-Whitney rank sum test was used to test for differences in anaesthetic score. Analysis of data was performed on a personal computer using SigmaStat (Jandel Scientific, California) software package. Significance was accepted at *P* < 0.05. The investigation was approved by the Ethics and Research Committees of the University of Pretoria.

### RESULTS

Intravenous administration of propofol to the midazolam group resulted in a median anaesthetic score of 1.5, com-

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Table 1: Anaesthetic score for individual changes in reflexes to evaluate anaesthetic depth after intravenous bolus administration of propofol at 4 mg/kg in bitches treated with midazolam or saline placebo.

Control group				Midazolam group			
No	Palpebral <sup>a</sup>	Eye <sup>b</sup>	Pedal <sup>c</sup>	No	Palpebral <sup>a</sup>	Eye <sup>b</sup>	Pedal <sup>c</sup>
1	1	0	0	5	1	1	0
2	0	0	0	6	0	1	0
3	0	0	0	7	0	1	0
4	0	0	0	8	1	1	0
Tscore <sup>d</sup>	1	0	0	2	4	0	

<sup>a</sup>Palpebral reflex, 0 = active; 1 = absent.

<sup>b</sup>Eye ball rotation, 0 = eye ball central (pedal reflex active); 1 = eye ball rotated down; 2 = eye ball central (palpebral reflex absent).

<sup>c</sup>Pedal reflex, 0 = active; 1 = absent.

<sup>d</sup>Total score.

pared to 0 in the control. The difference between the 2 groups was not significant. The mean incremental propofol dose required to obtain loss of the pedal reflex was 3.4 (0.8) mg/kg for the midazolam group, and 5.5 (0.8) mg/kg for the control group. The difference between the 2 groups was statistically significant ( $P < 0.05$ ). The pedal reflex returned after 3.5 (1.3) min in the midazolam group, and 4.8 (2.1) min in the control group. The time difference was not statistically significant. The minimum mean end-tidal isoflurane concentration (ETiso) for the midazolam and control groups to maintain loss of the pedal reflex during surgery were 1.7 % (0.3) and 2.2 (0.5) % respectively, a reduction of 23 %. The difference between the 2 groups appeared to be statistically significant ( $P < 0.05$ ), as it failed the normality and equal variance tests.

## DISCUSSION

Pre-induction administration of midazolam resulted in acute behavioural changes and decreased the propofol and isoflurane dose for surgical anaesthesia. The effects of the benzodiazepines on the behaviour of animals is of clinical relevance to the anaesthetist. Species differences in the behavioural effects are observed in animals after the administration of these agents. Contrary to the expected sedative-hypnotic effects as observed in humans<sup>15</sup>, pigs<sup>17</sup>, cattle<sup>11</sup> or goats<sup>19</sup>, excitatory effects may occur in cats<sup>6</sup>, dogs<sup>2</sup> and horses<sup>13</sup>. In this instance, increased motor activity associated with intense sniffing at their front legs or the induction table was observed in 3 animals within 60 sec of the intravenous administration of midazolam. This is in agreement with previous observations on the lack of sedative effects and altered behaviour after midazolam administration in dogs<sup>2</sup>. The highest density of benzodiazepine receptors is reported to be in the olfactory bulb<sup>11</sup> and may be partly responsible for the sniffing phenomenon. An appetite-stimulating effect in cats<sup>10</sup> and goats<sup>21</sup> was reported after benzodiaz-

epine administration. It is suggested that different benzodiazepine receptors may be responsible for the anxiolytic and sedative effects, and the affinity for the different receptor types may be responsible for the ability to produce sedation<sup>22</sup>. Anxiolysis and sedation are related to the percentage receptor occupation. The former is observed at lower occupation levels as opposed to sedation, which requires higher levels<sup>1</sup>. It is suggested that the species difference in the sedative-hypnotic effects of the benzodiazepines may be the result of species differences in the affinity of the agents for the benzodiazepine receptors. The lack of sedative effects and the stimulation of motor activity probably render these agents unsuitable for pre-anaesthetic sedation when administered on their own.

Intravenous administration of midazolam resulted in a decrease in the dose for both propofol and isoflurane to obtain loss of the pedal reflex. Although the pedal reflex is a pain reflex (noxious stimulation of the digit), no clinical analgesic qualities are associated with the systemic administration of these agents. However, benzodiazepine receptors occur in the spinal cord, and the epidural administration of diazepam is associated with analgesia<sup>8</sup>. In sheep, the systemic administration of midazolam results in an increase in the threshold for mechanical stimuli<sup>9</sup>. In humans, midazolam reduces the propofol dose required for sedation<sup>14</sup>, and to induce hypnosis and anaesthesia. The doses for the last 2 are reduced by 44 and 52 % respectively<sup>16</sup>. In dogs, a 12 % reduction in the thiethylal dose for tracheal intubation was observed after midazolam premedication<sup>5</sup>. In this investigation, a 37 % reduction in the anaesthetic dose (loss of pedal reflex) for propofol was obtained. Apnoea occurred only in the midazolam group<sup>20</sup>, and might indicate increased respiratory depression despite the reduction in the propofol dose. The effect on the dose for hypnosis was not evaluated. All the dogs were suitable for intubation after the administration of

propofol at 4 mg/kg. However, it appeared that a deeper plane of anaesthesia was obtained in the midazolam-treated group, as a score of 1.5 was obtained, which is in agreement with the apnoea observed in the group. The control group obtained a median score of zero. Differences in the endpoint for anaesthesia may be partly responsible for the difference in dose reduction compared to humans, and possible species differences are not excluded. Midazolam premedication resulted in the ETiso for surgical anaesthesia (loss of pedal reflex) to be reduced by 23 % in this investigation. The minimum anaesthetic concentration (MAC) for isoflurane in dogs<sup>18</sup> is 1.28 %. This represented a decrease from  $1.72 \times \text{MAC}$  for surgical anaesthesia in the control group to  $1.33 \times \text{MAC}$  in the midazolam-treated group. The intensity of noxious stimuli may vary during surgery, and this may have been partly responsible for the large intra-operative variation in ETiso to maintain loss of the pedal reflex.

It is concluded that midazolam premedication in dogs may reduce the dose required for surgical anaesthesia after propofol induction, and during isoflurane maintenance of anaesthesia. In addition, propofol administration may result in an induction apnoea, unless adjustments in dose or technique of propofol administration are made.

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