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Comparative Responses to Propofol Anaesthesia alone and with α_2-Adrenergic Medications in a Canine Model

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[1]Institute of Special Pathology and Clinical Surgery, College of Veterinary Medicine, University of Perugia, Perugia, Italy; [2]Department of Clinical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, New York, USA; [3]Institute of Hematology, College of Medicine, University of Perugia, Perugia, Italy; [4]Orion Corporation, Animal Health Division, Turku, Finland.

Bufalari, A., C. E. Short, C. Giannoni and O. Vainio: Comparative responses to propofol anaesthesia alone and with α_2-adrenergic medications in a canine model. Acta vet. scand. 1996, 37, 187-201. – Cardiovascular and pulmonary effects of propofol, a relatively new nonbarbiturate intravenous anaesthetic, were assessed and compared in 22 male and female dogs. Dogs in group 1 did not receive any premedication prior to 6.6 mg/kg IV propofol, group 2 was premedicated with atropine (0.02 mg/kg IM) and the α_2-agonist medetomidine (10 μg/kg IM), and group 3 received the same premedication agents as group 2, but the medetomidine effects were reversed by the α_2-antagonist atipamezole (30 μg/kg IV) after 30 min of anaesthesia. Each dog in groups 2 and 3 received a propofol induction dose of 2.2 mg/kg IV. The anaesthetic duration was shortest with propofol alone and prolonged with medetomidine as a premedication which was reversible with atipamezole. In group 1, the most prominent effects were a temporary drop in diastolic arterial blood pressure (26% and 24%) at 2 and 5 min post-propofol, respectively and a drop in respiratory frequency (41%) 2 min after propofol induction. Similar respiratory depression was observed in groups 2 and 3 (20% and 48%, respectively) at the same time. Apnea was not observed. An increase in systemic arterial blood pressure was observed throughout the trial in groups 2 and 3 until dogs recovered or were reversed with atipamezole. Medetomidine significantly reduces propofol dosage requirements. Safe and effective injectable anaesthesia was produced by propofol in this group of dogs. The frequency of respiratory depression would suggest in clinical usage, the practitioner should be aware oxygen supplementation is the treatment of choice should apnea occur.

medetomidine; atipamezole; injectable anaesthesia; canine; cardiopulmonary responses; analgesia; duration of propofol anaesthesia.

Introduction

Propofol (2,6-diisopropylphenol, Rapinovet®10mg/ml, Cooper Animal Health Ltd.) is a relatively new intravenous anaesthetic. It represents a new class of anaesthetic agents chemically unrelated to the barbiturate, imidazole, steroid, or eugenol agents. It is a member of the alkylphenol family. It was first utilized in animals in 1977 and was recently approved for veterinary use in Scandinavia. Because alkylphenols are oils at room temperature, they are only slightly soluble in water but highly in oils. For this reason the first formulation used Cremophor EL (BASF) as its vehicle. Unfortunately, this vehicle produced both anaphylactoid reactions *(Dye* 1980) and pain on injection

* These studies were completed at the College af Veterinary Medicine, Cornell University, Ithaca, New York, USA.

(Major 1981) and was immediately abandoned. The current formulation, used in our study and available in Scandinavia, consists of 1% propofol, 10% soybean oil, 2.25% glycerol and 1.2% purified egg phosphatide. This preparation limits the use of propofol to intravenous (IV) injection. This new formulation for propofol has some minor side effects, i.e. pain on injection reported both in a few human patients *(Klement & Arndt* 1991) and in some animals *(Weaver* 1990). *Klement & Arndt* (1991) concluded from their study that the intensity of pain during intravenous propofol injection was linked to its free aqueous concentration.

Propofol, as a short acting agent for anaesthetic induction and maintenance, has many desirable features *(Langley et al.* 1988). Propofol anaesthesia is characterized by rapid onset, rapid hepatic metabolism, lack of accumulation on repeated administration, and absence of excitatory effects on induction during maintenance and recovery *(Biebuyck* 1989). It has also been used as a sedative in patients undergoing treatment in Intensive Care Units, diagnostic procedures *(Langley* 1988), and orthopedic surgery with regional anaesthesia *(Mackenzie* 1987). It has been used concurrently with different drugs in premedicated and nonpremedicated dogs and cats *(Watkins* 1987). Variable anaesthetic properties have been observed with these combinations, since premedication can alter CNS, cardiopulmonary or metabolic processes during anaesthesia.

Medetomidine (Domitor®; Orion Corporation – Animal Health Division) is an α_2-adrenoceptor agonist with sedative and analgesic properties in dogs and cats *(Short* 1992). Medetomidine has already been used in combination with propofol infusion *(Vainio* 1991) and propofol bolus *(Hammond* unpublished data) and with anticholinergic premedication *(Vainio* 1989) in dogs.

Atipamezole (Antisedan®; Orion Corporation Animal Health Division) is a specific α_2-adrenoceptor antagonist. It is used to reverse the sedation, analgesia, and side effects of medetomidine *(Short* 1992, *Young* 1990, *Vainio* 1990, *Vähä-Vahe* 1990) in dogs. Usually an intramuscular dose of atipamezole 5 times as much as the previous dose of medetomidine gives effective reversal of the agonist. The dose of atipamezole is often reduced to 3 times the medetomidine, if the antagonist is administrated by intravenous route when more rapid recoveries are desired.

Atropine sulfate (Anpro Pharmaceuticals) is a frequently used parasympathetic antagonist with specific antimuscarinic action. Even though glycopyrrolate may be the drug of choice in a number of hospitals, atropine is a widely available medication. It has been used as a preanaesthetic agent prior to propofol anaesthesia both in human patients *(Sneyd* 1991) and in dogs.

The first objective of this study was to determine the anaesthetic properties and the cardiorespiratory changes mediated by the administration of propofol as sole agent for comparison to its use with a preanaesthetic. Since medetomidine, a potent α_2-agonist, is widely used in the Nordic countries and has significant influence on responses mediated by anaesthesia, the second objective was to determine the influence of atropine and medetomidine on the anaesthetic properties and cardiovascular changes of propofol. The third objective was to develop a safe anaesthetic protocol that could lead to a fast and smooth recovery, if medetomidine premedication prolonged anaesthesia or if anaesthetic complications resulted from medetomidine-propofol concurrent usage and the index to the effect of medetomidine on the recovery period. The combination of these objectives should provide the practitioner with guidelines for use of the medications and noninvasive monitoring *(Sawyer et al.* 1991) during clinical anaesthesia.

Materials and methods

Twenty-two purpose bred dogs, 11 females and 11 males, were used. All dogs were in excellent health as determined by physical examination. As a result, their physical status was ASA 1 in accordance to the classification system of the American Society of Anesthesiologists indicating no expected anaesthetic risk. The age of the dogs ranged from 15 to 20 months and the average weight was 21 kg (range 16.6 to 25.2 kg). The animals were kept in appropriately sized kennels in a variable number of 2 or 3 per group, fed a commercial diet with continuous access to water, regularly dewormed and vaccinated. The fasting period preceding experimentation began the evening prior to inclusion in trials the next day and lasted a minimum of 6 h and a maximum of 16 h. Animals were randomly divided into group 1 (10 dogs); group 2 (6 dogs); and group 3 (6 dogs) and assigned to the experimental protocol. Every group included an equal number of females and males to nullify any effect of sex on the statistical analysis.

Group 1: Propofol alone was given intravenously (IV) as a slow injection (60 seconds) at a dose rate of 6.6 mg/kg.

Group 2: Atropine was administered for premedication at a dose of 0.02 mg/kg (IM). A dose of 10 μg/kg (IM) medetomidine was given 5 min after atropine. Propofol was injected intravenously (IV) as a slow injection (45 seconds) approximately 18 min after atropine at a dose of 2.2 mg/kg.

Group 3: The same protocol as group 2 was used except that atipamezole was administrated intravenously (IV) at a dose rate of 30 μg/kg (3 times medetomidine dose) immediately after the 30 min recordings were completed. Nineteen of the 22 dogs were intubated as soon as general anaesthesia was induced and adequate relaxation of the masseter muscles was accomplished.

The ECG was monitored by a Datascope 870 and recorded on a Datascope 721A. Pulse rate and blood pressure (systolic, diastolic and mean) responses were monitored using a noninvasive pressure monitor (Dinamap 1846 SX/P, Critikon). The cuff was placed around the metatarsal region above a perceptible artery. Three cuff sizes were available to provide selection of the most appropriate size in order to comply with manufacturer's guidelines. Noninvasive techniques were used to avoid excessive restraint of awake dogs and to provide immediate data following anaesthetic induction. The use of atropine maintains heart rates at a higher level following medetomidine and reduces the problems of noninvasive blood pressure monitoring.

Respiratory rates and airway carbon dioxide levels were recorded using a HP47210A capnometer (Hewlett-Packard) connected to the endotracheal tube during anaesthesia or mask during recovery. Oxygen saturation was measured by a pulse-oximeter Model (501+, Criticare Systems). The sensitive probe was placed on the lateral surface of the tongue of each dog. This was used to assure that adequate levels of oxygen were available to tissues.

The following serum evaluations were performed by the Clinical Pathology Laboratory at the Cornell Veterinary College: sodium, potassium, chloride, total carbon dioxide, calcium, phosphorus, total protein, albumin, globulin, albumin/globulin, urea nitrogen, creatine phosphokinase (CPK), glucose, cholesterol, lipase, ALT, AST, alkaline phosphatase, total bilirubin, and Na:K ratio.

The following hematological evaluations were completed by the same laboratory: hematocrit, red blood cell count (RBC), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell count (WBC) and ra-

tios, segmented neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets, and total protein. Results were compared to standard values in published tables *(Short* 1987). These values were previously determined as normal ranges in the dog with the equipment and techniques used as standard operation for the laboratory. The samples were drawn the day before anaesthesia and immediately submitted for analysis.

The protocol was approved by the University Animal Use Committee and conducted utilizing GLP (Good Laboratory Practice) standards in facilities approved by the American Association of Laboratory Animal Care.

Multiple comparisons were performed between anaesthetic groups and within each anaesthetic group. Values recorded before anaesthesia (predrug) were used as control. The significance of differences was tested by analysis of variance (ANOVA) two factors and Bonferroni test *(Altman* 1991). A 95% confidence level was considered significant ($p<0.05$).

All parameters in the protocol for this study, pulse rate, blood pressure, ECG, respiratory rate, and related parameters, were recorded as scheduled to determine control, 2 min post-induction of anaesthesia, and 5 min interval data. Expired carbon dioxide and oxygen saturation were measured starting 2 min after propofol administration. These measurements were continued at 5, 10, 15, 20, 25, and 30 min after propofol injection, or until the dogs would not tolerate the sensor probe on the tongue. In groups 2 and 3, pulse rate, indirect blood pressure, temperature, ECG, and respiratory frequency were measured before propofol administration: predrug (control), premedetomidine (4 min after atropine bolus), and prepropofol (14 min after medetomidine injection). End expired carbon dioxide levels and oxygen saturation were recorded respectively prepropofol, 2 min post-propofol, and continued at 5 min intervals as long as the dogs would tolerate the probes. Awake control values for carbon dioxide and oxygen saturation were not achieved, since the recording technique required a sedated or anaesthetized subject. In group 3 data were recorded at 2 and 5 min after atipamezole injection.

The stage of anaesthesia was assessed by evaluating the response to mechanical noxious stimulus (tail clamp) and the palpebral reflexes. The noxious stimulus was created by engaging a noncrushing intestinal forceps to the first serration on the lock across the tail for no more than 3 sec. The palpebral reflex evaluation was accomplished by touching the medial canthus of the upper eyelid with a finger tip. The return of normal reflexes was considered to be the end of anaesthesia; rising the head was considered the emergence stage 1; sternal recumbency was judged emergence stage 2, and voluntary standing was considered as measurable recovery from propofol.

Results

No significant metabolic and hematologic abnormalities that would affect the final results were seen in either group of dogs. In all groups recumbency from induction of anaesthesia was observed during the 45 to 60 sec propofol injections without excitatory effects, such as hypertonus, myoclonia or involuntary movements. Induction time was within 15 sec with or without preanaesthetic medetomidine; however, propofol dosage was reduced in dogs receiving medetomidine.

In group 1 intubation was easy and without complications in all dogs. No cases of excessive salivation or vomiting were observed. During general anaesthesia, none of the 10 dogs responded to cross-clamp on the tail. Except for one dog that had a brief period of paddling and limb stiffness (barbiturate pattern), recovery

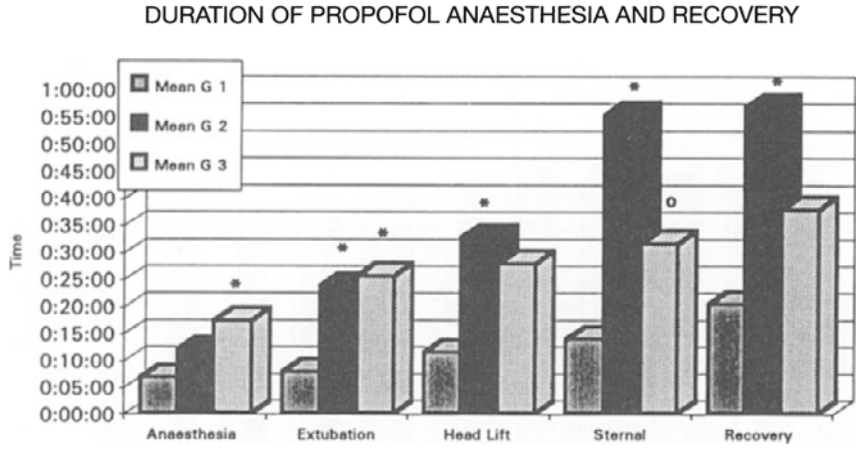

Figure 1. Mean values from induction time to end of anaesthesia, extubation, head lift, resumption of sternal recumbency and standing. *Statistically significant difference ($p<0.05$) from group 1. ○ Values in group 3 significantly lower ($p<0.05$) than group 2. Group 1 – propofol 6.6 mg/kg IV. Group 2 – medetomidine 10 μg/kg IM, propofol 2.2 mg/kg IV. Group 3 – medetomidine 10 μg/kg IM, propofol 2.2 mg/kg IV, atipamezole 30 μg/kg IV at 30 min.

was rapid, smooth and without excitement. In group 2, two dogs were not intubated because of persisting laryngeal reflex, and one of them did not reach an adequate level of surgical anaesthesia from the initial 2.2 mg/kg dosage of propofol administered. This dog returned to standing position at 8 min and 51 sec. The others took more time for standing, but the recovery was invariable smooth and calm.

In group 3, one dog, even though recumbent, did not reach a plane of anaesthesia considered sufficient for surgical procedures, but was judged adequate for diagnostic approaches. It was not intubated. A higher propofol dose would have been required to induce surgical anaesthesia. It was not given to allow comparison of all dogs within the groups at the same dosage levels. One case of rapid, shallow respiration was observed at the following time intervals: 10 and 25 min after propofol bolus and 5 min after atipamezole administration.

The influence of medetomidine on anaesthesia reversal by atipamezole was evident within 2 min. In 3 dogs it was impossible to record more data after reversal. The most noticeable response was a return of activity in the dogs and the lowering of mean arterial blood pressure by up to 35% (mean value) (Figs. 2, 3, and 4). The first signs of arousal were tail movements and head lifting. Sternal recumbency was within 7 min. Recovery of each dog was fast, smooth and without excitement or complication. Dogs were able to walk within 9 min with slight signs of ataxia and walk normally within 15 min after the antagonist injection (Fig 1). The duration of anaesthesia was longer in group 2 and 3 than with propofol 6.6 mg/kg as sole agent (Fig 1). All dogs, especially in group 1, appeared friendly, curious, and interested in their surroundings after awaking.

Group 1: The average mean arterial blood pressure decreased slightly after the propofol bolus injection (Fig 2). At 2 min post propofol administration, the blood pressure dropped from 99.2 ± 22.6 mm Hg (predrug value) to 86.2 ± 11.9 mm Hg (mean ± sd). Within 10 min

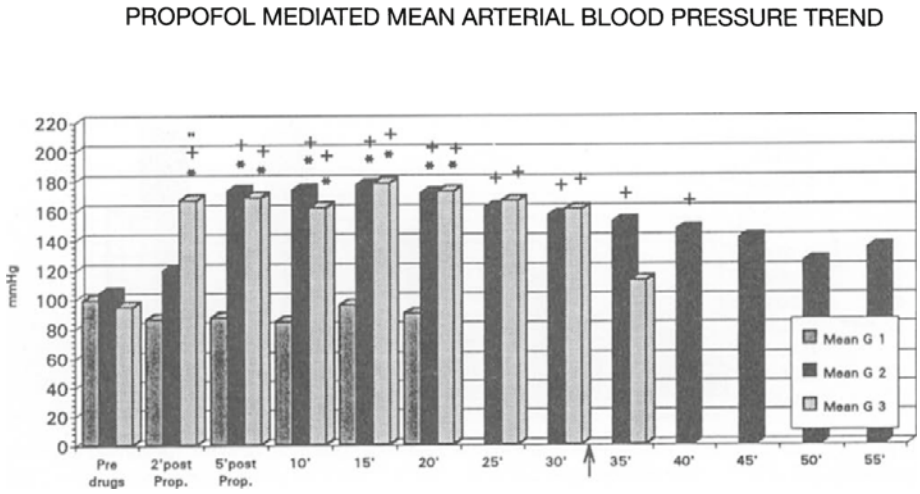

Figure 2. Mean values for mean arterial blood pressure during anaesthesia (groups 1 and 2) and until 2 min after atipamezole bolus (group 3).$^{+}$ *Statistically significant difference ($p<0.01$) compared to group 1; $^{+}$statistically significant difference ($p<0.05$) compared to predrug controls (predrugs); $''$values in group 3 significantly higher ($p<0.05$) than group 2. Group 1 – propofol 6.6 mg/kg IV. Group 2 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM and medetomidine 10 μg/kg IM; premedication). Group 3 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM, medetomidine 10 μg/kg IM; premedication, atipamezole 30 μg/kg IV; post-anaesthesia). Prop = propofol; $\uparrow$ = atipamezole administration.

it decreased to 84.4 ± 12.9 mm Hg (minimum value) and remained below, but not significantly less than the prepropofol level.

Group 2: Average values of the arterial blood pressure 8 min after medetomidine injection were: 158.3 ± 30.4, 128.3 ± 33.2 and 108.3 ± 31.3 mm Hg for systolic, mean and diastolic blood pressure respectively. After a slight reduction 2 min post-propofol (119.7 ± 9.5 mm Hg), mean arterial blood pressure returned to the higher values (177.2 ± 14.9 mm Hg, maximum recorded value) and persisted above the prepropofol level until the dogs were capable of standing.

Group 3: Average values of the mean arterial blood pressure remained stable after atropine injection, but increased 8 min after medetomidine administration to 139 ± 36 mm Hg (Fig 2). Another increase in the mean arterial blood pressure was observed 2 min after propofol bolus injection (167 ± 18 mm Hg), and the peak was reached 15 min after propofol bolus (178 mm Hg). Mean arterial blood pressure values remained above the prepropofol level until atipamezole was administered. Blood pressures were significantly higher in groups 2 and 3 during medetomidine/propofol compared to control ($p<0.05$). Blood pressures were also significantly greater ($p<0.01$) in groups 2 and 3 compared to group 1 (Figs 2, 3, and 4) during propofol anaesthesia.

In group 1 no significant changes were observed in mean pulse rate, and it remained within normal limits throughout the study.

In groups 2 and 3 pulse rates decreased unexpectedly during the first 13 min following atropine premedication. The lowest levels recorded (mean ± sd) were 77 ± 14 beats/min at 13 min

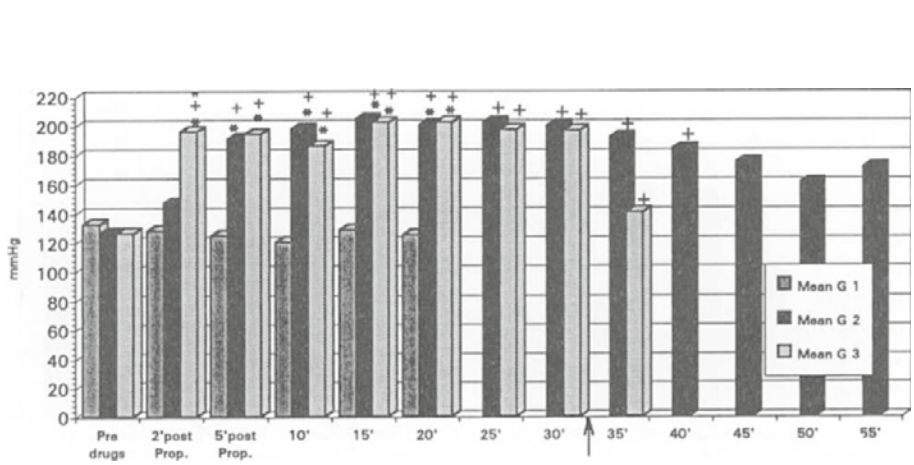

Figure 3. Mean values for systolic arterial blood pressure during anaesthesia (groups 1 and 2) and until 2 min after atipamezole bolus (group 3).$^{+}$ *Statistically significant difference ($p<0.01$) compared to group 1; $^{+}$statistically significant difference ($p<0.05$) compared to predrug controls (predrugs); ″values in group 3 significantly higher ($p<0.05$) than group 2. Group 1 – propofol 6.6 mg/kg IV. Group 2 = propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM and medetomidine 10 μg/kg IM; premedication). Group 3 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM, medetomidine 10 μg/kg IM; premedication, atipamezole 30 μg/kg IV; post-anaesthesia). Prop = propofol; ↑ = atipamezole administration.

(group 2) and 71 ± 31 beats/min at 4 min (group 3) after atropine administration. Then they elevated reaching a maximum value of 149 ± 17 in 10 min (group 2) and 155 ± 33 beats/min at 5 min (group 3) after injection of propofol. A consistent drop in heart rate occurred 10 min after propofol administration and persisted. There were no significant differences between the groups (Fig 5), and the drops were not considered as clinical concern.

Group 1: The respiratory frequency increased during the anaesthetic induction phase. At 2 min following propofol bolus injection, a consistent but insignificant drop in respiratory rate was recorded. The minimum mean level was 12.6 breaths/min (8.6 breaths/min less than baseline value). This was followed by a return to a normal physiologic respiratory pattern. It was not possible to obtain consistent prepropofol carbon dioxide data by face mask for comparison to the endotracheal data obtained during anaesthesia.

Group 2: The highest value (22.7 ± 4.8 breaths/min) was recorded prior to any medication (control). A decrease in frequency was noticeable 2 min before propofol injection and after the propofol effect. The lowest value was 7.4 ± 1.5 breaths/min at 40 min after the induction was completed.

Group 3: The maximum respiratory rate recorded was 25.7 ± 7.8 breaths/min at 8 min after medetomidine injection. While a consistent drop occurred after propofol injection, the lowest value was observed at 5 min post-propofol (11.1 ± 2.5 breaths/min). There were no significant differences between groups (Fig 6).

In groups 2 and 3, carbon dioxide concentration in the expired air increased after propofol in-

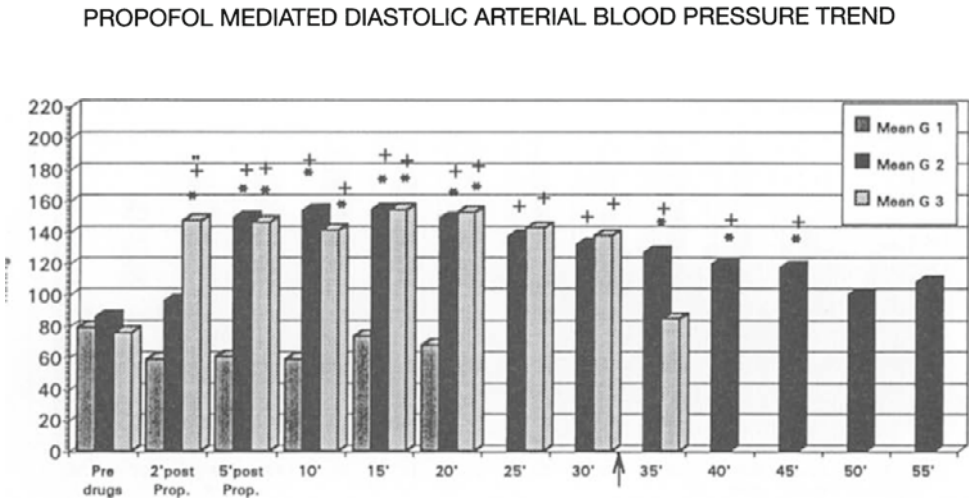

Figure 4. Mean values for diastolic arterial blood pressure during anaesthesia (groups 1 and 2) and until 2 min after atipamezole (group 3).$^{+}$ *Statistically significant difference ($p<0.01$) compared to group 1; $^{+}$statistically significant difference ($p<0.05$) compared to predrug controls (predrugs); ″values in group 3 significantly higher ($p<0.05$) than group 2. Group 1 – propofol 6.6 mg/kg IV. Group 2 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM and medetomidine 10 μg/kg IM; premedication). Group 3 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM, medetomidine, 10 μg/kg IM; premedication, atipamezole 30 μg/kg IV; post-anaesthesia). Prop = propofol; ↑ = atipamezole administration.

duction and remained above the level recorded after medetomidine administration throughout the procedure. The higher concentrations were peaked at 10 and 15 min after propofol administration (35 mm Hg).

In group 1, carbon dioxide decreased slightly 10 min after propofol administration (following the respiratory trend) and remained between 30 and 32 mm Hg throughout anaesthesia. There were no significant differences within and between the groups except at 5 min after intubation when only propofol was used (Fig 7). The mean values of the oxygen saturation in group 1 varied from a minimum of 89.6 ± 4.1% to a maximum of 95.2 ± 2.9% at 2 and 15 min post-propofol, respectively. In group 2 they varied from 82.6 ± 4.7% to 90.8 ± 1.1% at 2 and 25 min after propofol injection. In group 3 average values varied from 86.0 ± 5.7% at 10 min to 91.8 ± 2.9% at 30 min after propofol injection. There were no significant differences between the groups (Fig 8). All dogs received oxygen administration for a variable time during anaesthesia to improve oxygen saturation when the pulse oximeter readings dropped below 90% after the 2-min reading. Desirable oxygen saturation was, therefore, maintained throughout anaesthesia as a result. Oxygen supplementation was not necessary during recovery in any of the dogs.

The duration of anaesthesia was considered as the period of time between the end of propofol administration and the response to the tail clamping and palpebral touching (Fig 1). The mean duration of anaesthesia (min:sec) was 6:41 ± 3:08 (group 1), 12:01 ± 6:53 (group 2), and 17:22 ± 7:02 (group 3). The mean times of extubation in groups 1, 2, and 3 were 7:52,

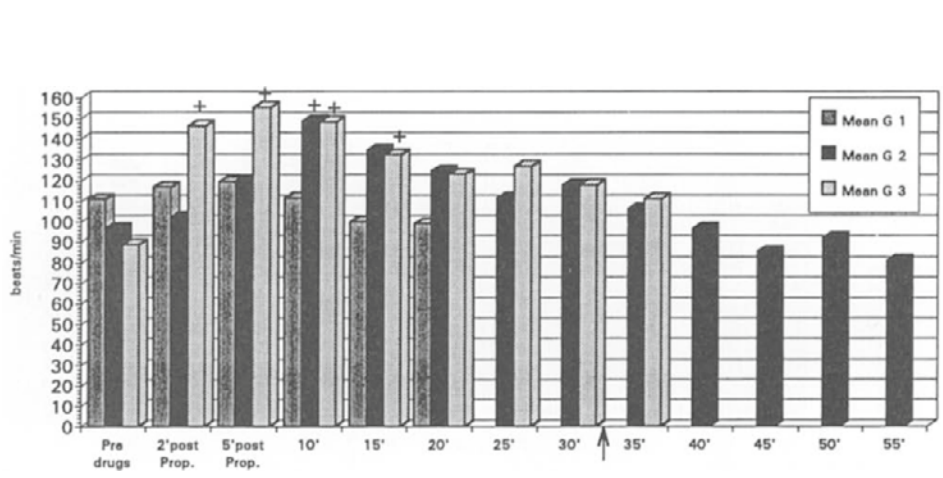

Figure 5. Mean values for pulsations/minute during anaesthesia (groups 1 and 2) and until 2 min after atipamezole bolus (group 3). Statistically significant difference ($p<0.05$) compared to group 1; and to predrug controls (predrugs). Group 1 – propofol 6.6 mg/kg IV. Group 2 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM and medetomidine 10 μg/kg IM; premedication). Group 3 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM, medetomidine 10 μg/kg IM; premedication, atipamezole 30 μg/kg IV; post-anaesthesia). Prop = propofol; ↑ = atipamezole administration.

23:47 and 25:37, respectively. Dogs in group 1 lifted the head at 11:27 (mean time), while the premedicated dogs reached emergence stage 1 at 32:41 (group 2), and 27:56 (group 3). The administration of atipamezole after the end of anaesthesia reversed the effect of medetomidine and significantly reduced the time to sternal or standing compared to the medetomidine group where sedation was allowed to continue.

Discussion

The present study was designed for determination of the physiological changes occurring during anaesthesia with propofol alone and as influenced by combination with other drugs (atropine, medetomidine, atipamezole). The duration of anaesthesia was evaluated and its reversal with atipamezole compared to propofol as a sole agent and propofol plus medetomidine in order to determine if the longer lasting effects were due to propofol or medetomidine.

The cardiovascular effects of propofol as the only anaesthetic agent have been measured in several studies *(Miller* 1990). Propofol used for both induction and maintenance of anaesthesia has caused a drop in systemic blood pressure attributed to both vasodilatation *(Sebel et al.* 1989, *Claeys et al.* 1983) and a decrease in cardiac output/cardiac index and stroke volume index *(Coates et al.* 1987). Nevertheless, *Goodchild et al.* (1989) consider the cardiac output decrease a result of reduction in preload by a direct venodilator effect. However, peripheral vasodilatation studies conducted by *Nakamura et al.* (1992) in isolated dog arteries demonstrated that clinically relevant concentration of propofol did not have direct vasodilator consequences.

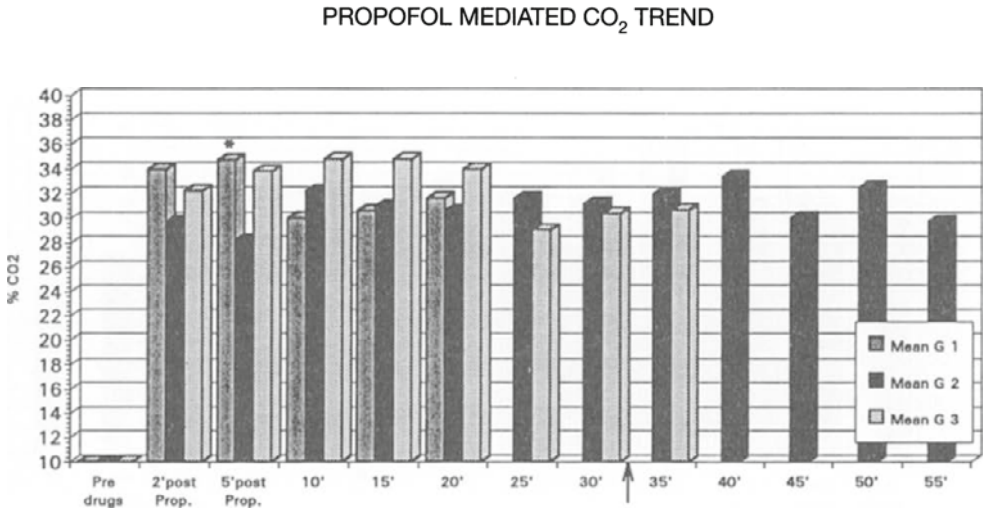

Figure 6. Mean values (± sd) for carbon dioxide during anaesthesia (groups 1 and 2) and until 2 min after atipamezole bolus (group 3). *Statistically significant difference ($p<0.05$) compared to group 1. Group 1 – propofol 6.6 mg/kg IV. Group 2 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM and medetomidine 10 μg/kg IM; premedication). Group 3 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM, medetomidine 10 μg/kg IM; premedication, atipamezole 30 μg/kg IV; post-anaesthesia). Prop = propofol; ↑ = atipamezole administration.

A drop in systemic pressure during induction of anaesthesia has been reported as a 25% to 40% reduction of systolic blood pressure at dosages of 2 mg/kg *(Grounds et al.* 1985, *Claeys et al.* 1983). In our present study, propofol (6.6 mg/kg, group 1) decreased the indirect systolic arterial blood pressure by 3.5% and 5.9%, respectively at 2 and 5 min post-propofol, the mean arterial pressure by 13% (2 min) and 12% (5 min), and the diastolic arterial pressure by 25.9% and 23.7% at the same intervals of time. This was probably due to vasodilatation.

Except during the early induction phase where a marked, transient increase in heart rate was observed, propofol did not significantly change pulse rates in this study despite decreased arterial pressure. In this respect, propofol appears to allow a noticeable resetting of the reflex set point without depressing the baroreflex sensitivity, *Cullen* (1987). No significant cardiac dysrhythmias were observed. Bradycardia induced by the medetomidine premedication is a classic feature of α_2-agonist agents. The direct action of medetomidine on the post synaptic α_2-receptors of the vascular smooth muscle leads to vasoconstriction and an initial transient hypertension followed by pronounced bradycardia while later hypotension may be observed. The decrease in heart rates may be in the form of sinus bradycardia or, rarely, an atrioventricular (A-V) block may be observed *(Short* 1992). To prevent these unwanted effects, atropine (0.02 mg/kg) was chosen as the anticholinergic premedication to medetomidine due to its well known properties and previous use in conjunction with medetomidine *(Bergström* 1988). However, *Dunckle et al.* (1986), in an echocardiographic study in cats, showed that anticholinergic medication could have damaging effects on cardiac performance. In this study additional factors should be considered. Propofol as a sole agent may cause a

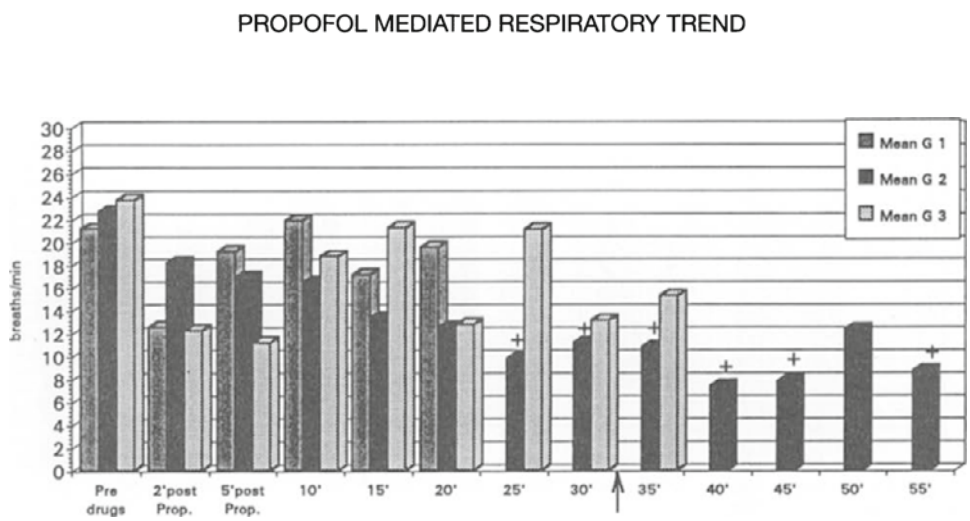

Figure 7. Mean values for breaths/minute during anaesthesia (groups 1 and 2) and until 2 min after atipamezole bolus (group 3). $^{+}$Statistically significant difference ($p<0.05$) compared to predrug controls (predrugs). No significant differences between groups. Group 1 – propofol 6.6 mg/kg IV. Group 2 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM and medetomidine 10 μg/kg IM; premedication). Group 3 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM, medetomidine 10 μg/kg IM; premedication, atipamezole 30 μg/kg IV; post-anaesthesia). Prop = propofol; $\uparrow$ = atipamezole administration.

trend toward reduced blood pressure and increased heart rate. This is the opposite responses as observed with medetomidine. In the dogs receiving atropine/medetomidine followed by propofol, hypertension was not as severe nor lasted as long as may be observed in atropine-medetomidine treated dogs. In these young, healthy dogs, the cardiovascular effects of combined atropine/medetomidine premedication was considered safe.

In contrast to *Bergström's* report (1988), we did not observe severe bradycardia or other dysrhythmia after the administration of a combination of atropine-medetomidine, but notable increases in the indirect mean arterial blood pressure (23% and 46.6%) were noted in groups 2 and 3, respectively. This trend persisted after propofol injection with a sharp increase manifested 5 min after propofol bolus. This could lead one to the conclusion that propofol in combination with atropine-medetomidine as premedication drugs has a hypertensive effect in dogs persisting until spontaneous arousal (group 2) or atipamezole assisted arousal (group 3). However, propofol alone does not mediate this hypertensive effect. α_2-Agonists increase peripheral vascular resistance. Observation of clinical procedures in Europe shows these changes with propofol-medetomidine are not as likely to occur if propofol is administered immediately after medetomidine *(Stauffer* 1995, personel communication).

Chronotropic effect could be related more to the synergism of propofol and atropine-medetomidine in this group of dogs than to indirect central effect or direct effect on the heart muscle as proposed by *Vainio* (1991). In fact, our preliminary studies, conducted on the effect of medetomidine as a sedative/analgesic on propofol anaesthesia, revealed a noneffective influence of propofol on the medetomidine mediated bradycardia.

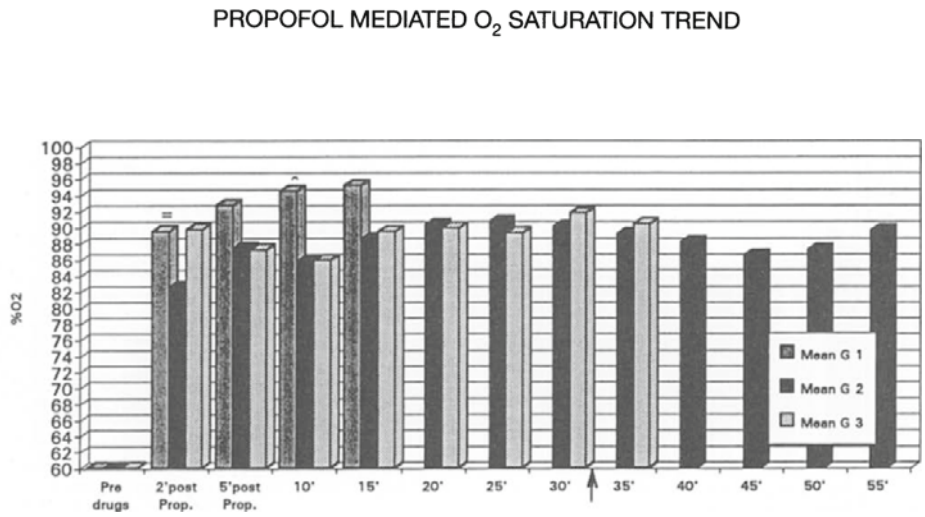

Figure 8. Mean values for oxygen saturation during anaesthesia on room air (groups 1 and 2) and until 2 min after atipamezole bolus (group 3).+ Statistically significant difference ($p<0.05$) compared to group 2. Significant difference ($p<0.05$) compared to groups 2 and 3. Group 1 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM and medetomidine 10 μg/kg IM; premedication). Group 3 – propofol 2.2 mg/kg IV (atropine 0.02 mg/kg IM, medetomidine 10 μg/kg IM; premedication, atipamezole 30 μg/kg IV; post-anaesthesia). Following readings <90% oxygen, supplemental oxygen was administered until values equal to or greater than 90%. Prop = propofol; ↑ = atipamezole administration.

As shown in the literature *(Smith et al.* 1993), the ventilatory effects of propofol were qualitatively similar as those seen with other intravenous induction agents or may be more severe if rapid injections of propofol are used. The rapid and shallow respiratory pattern propofol mediated during the induction phase could be related to the changes in the state of the CNS between wakefulness and anaesthesia. Propofol mediated tachypnea is usually accompanied by a reduction in tidal volume *(Goodman* 1987). The respiratory depression within the first minutes after propofol administration could be due to a suppression in the central inspiratory system activity. The respiratory frequency dropped by 40.5% (group 1), 19.8% (group 2), and 48.1% (group 3) less than prepropofol values at 2 min after propofol injection. However, no cases of apnea were observed (for the purpose of this research, we defined apnea as interruption of the respiration greater than 60 sec duration). Early reduction in respiratory volume probably accounted for reduction in oxygen saturation. The mean value of expired carbon dioxide tension stayed within acceptable limits in all groups. The capnometer used is reported to correlate well with arterial carbon dioxide partial pressures *(Whitesell et al.* 1981). The initial drop in ventilation at induction contributed to a reduction in oxygen saturation. This was followed by slight hyperventilation probably contributing to reduction in carbon dioxide. The use of oxygen-enriched inspired air, especially in groups 2 and 3, was beneficial to maintain oxygen saturation at adequate levels when it dropped below 90% of saturation.

The use of 90% oxygen saturation as a guide to supplementation of oxygen establishes a high

standard of ventilation. This level assures that any adverse response is unlikely to be caused by poor ventilation. All values were recorded on room air. Since the values less than 90% were not critical, oxygen was administered until 90% was reached. This provided the opportunity to access the duration of respiratory depression. The most likely complication associated with propofol in this study was reduced ventilation. In practice, the veterinarian is advised to make sure that the dogs have adequate ventilation during propofol anesthesia. Should hypoxemia occur, the treatment of choice is oxygen supplementation. If not available, restoration of respiratory volume with room air by assisted breathing is the next logical choice of treatment. No cases of emetic sequelae (vomiting) were observed in this study either immediately after recovery or 4 h post-anaesthesia.

In spite of longer duration of anaesthesia, the 2.2 mg/kg propofol dose in group 2 was not considered adequate to intubate 2 dogs. Additional propofol 1.1 mg/kg at 2 min after the initial dose was used to establish the desirable level of anaesthesia. Medetomidine may significantly influence the propofol available to the CNS by its effect on cerebral circulation. It has been shown that medetomidine at variable dosages can reduce cerebral blood flow by up to 60% *(Short* 1991). Dexmedetomidine, an isomer of the medetomidine racemic combination, was also shown to reduce CBF up to 50% in dogs *(Karlsson* 1990, *Zornow* 1990). The dosage requirements are significantly reduced. Appropriate consideration of dose and rate of administration were very effective in this study to prevent reported apnea from rapid injection or failure to reduce propofol dosage in premedicated dogs *(Smith* 1993).

Conclusions

The 6.6 mg/kg IV dose of propofol given to nonpremedicated dogs induced short duration anaesthesia 6.41 min (mean time) without excitatory phenomena. The ventilatory depressant effects of propofol were undeniable, but could be easily managed in clinical practice. Recovery characteristics were desirable especially when compared to thiopental. There was rapid emergence and minimal post-anaesthetic confusion or ataxia in propofol treated dogs.

In dogs premedicated with atropine and medetomidine, the 2.2 mg/kg (IV) dose of propofol proved a promising new regimen for anaesthesia lasting 15 to 20 min. Some dogs may require up to 3.3 mg/kg for induction. Changes in heart rates and blood pressure remained within acceptable limits. The use of oxygen-enriched inspired air was beneficial to increase the oxygen saturation. Medetomidine extended the duration of propofol anaesthesia and provided post-anaesthetic sedation/analgesia.

The use of the atipamezole resulted in a safe, smooth and fast reversal of the more prolonged recoveries observed when medetomidine was used as a preanaesthetic without reversal. Reversal also completely reduced post-anaesthetic analgesia. This confirmed the influence of medetomidine on the recovery from propofol. Absence of side effects and controllability in this group of dogs demonstrated propofol is a clinically useful intravenous drug for induction of anaesthesia with associated rapid and safe recovery.

This study has demonstrated the choice of propofol alone or in conjunction with α_2-adrenergic agents provide selective protocols for anaesthetic management in the dog depending on patient needs.

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Sammandrag

Jämförelse av respons till enbart propofol-anestesi och efter α_2-adrenergisk premedicinering i en hundmodell.

De kardiovaskulära och lungrelaterade effekterna av propofol, ett föhållandevis nytt intravenöst anestesimedel utan barbiturater, utvärderades och jämfödes hos 22 hundar (hannar och tikar). Hundarna i grupp 1 premedicinerades inte före administration av 6,6 mg/kg propofol i.v., grupp 2 premedicinerades med atropin (0,02 mg/kg i.m.) och α_2-agonisten medetomidin (10 μg/kg i.m.) och grupp 3 fick likadan premedicinering som grupp 2, men medetomidineffekten reverserades med α_2-antagonisten atipamezol (30 μg/kg i.v.) efter 30 min anestesi. Varje hund i grupp 2 och 3 fick propofol i.v. i dosen 2,2 mg/kg som induktion. Den kortaste sömngivande effekten erhölls med enbart propofol; anestesin varade längre efter premedicinering med medetomidin och kunde då reverseras med atipamezol. I grupp 1 var de mest påfallande effekterna en övergående sänkning av det diastoliska artärtrycket (26% och 24%) 2 respektive 5 min efter administration av propofol samt lägre andningsfrekvens (41%) 2 min efter propofolinduktion. En jämförbar andningsdepression konstarterades i grupp 2 och 3 (20% och 48%) vid samma tidpunkt. Ingen apné konstaterades. En ökning av det systemiska artärtrycket observerades generellt under försöket i grupp 2 och 3 tills djuren återhämtat sig eller reverserats med atipamesol. Med medetomidin behövs signifikant lägre dos av propofol. I denna grupp hundar erhölls säker och effektiv anestesi med intravenöst givet propofol.

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