Comparison of alfaxalone and propofol administered for total intravenous anaesthesia during ovariohysterectomy in dogs

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DEDICATIONS

To my wife Macarena
Thank you for support and understanding

To my mother and father Maria and Carlos
Thank you for being always with me, even when you are far away

Summary

Objective To compare the anaesthetic and cardiopulmonary effects of alfaxalone in comparison to propofol when used for total intravenous anaesthesia (TIVA) during ovariohysterectomy in dogs.

Animals Fourteen healthy female crossbred dogs between 6 months and 5 years, with body weight between 16 - 42 kg.

Methods All dogs were premedicated with acepromazine 0.01 mg/kg and morphine 0.4 mg/kg subcutaneously. Anaesthesia was induced and maintained with either Group 1- propofol (6 mg/kg followed by 0.3-0.5 mg/kg/min intravenously) or Group 2 alfaxalone (2 mg/kg followed 0.10-0.12 mg/kg/min intravenously). Quality of induction and recovery were determined. Dogs were spontaneously breathing 100 % oxygen. Respiratory and cardiovascular parameters were measured: Respiratory rate (RR), end tidal CO_2 ($ETCO_2$), tidal volume (TV). Heart rate (HR), systolic (SAP), diastolic (DAP), and mean arterial blood pressure (MAP). Arterial blood samples were collected during and after the surgery to determinate arterial PH, $PaCO_2$, PaO_2.

Results Smooth and rapid induction followed by satisfactory maintenance and good recovery quality was observed with both anaesthetic agents. Cardiopulmonary effects were similar for both groups with notable respiratory depression and fair hemodynamic parameters.

Conclusions and Clinical Relevance The administration of alfaxalone used as TIVA in premedicated dogs produced satisfactory anaesthesia with the same quality as that produced by propofol during ovariohysterectomy. Hypoventilation was the most prominent adverse effect from both anaesthetic agents suggesting a need for ventilatory support during prolonged TIVA periods with either anaesthetic agent.

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Chapter 1: Introduction

1.1 Anaesthesia

The word anaesthesia was used many centuries before its use for pharmacological and scientific phenomena (Askitopoulou et al. 2000). The term anaesthesia, derived from the Greek term *anaisthaesia*, meaning "insensibility", is used to describe the loss of sensation to the entire or any part of the body (Thurmond and Charles 2007). Anaesthesia is induced by drugs that depress the activity of nervous tissue locally, regionally, or within the central nervous system (CNS). General anaesthesia is drug-induced unconsciousness that is characterized by controlled but reversible depression of the CNS and analgesia. In this state the patient is not arousable by noxious stimulation. Sensory, motor, and autonomic reflex functions are attenuated. The anaesthetic state is normally induced by inhalation or injection techniques. By inhalation anaesthetic gases or vapor are inhaled in combination with oxygen. Anaesthetic solutions can be administered by injection, intravenously, intramuscularly, and subcutaneously. Other infrequently used injectable routes include intrathoracic and intraperitoneal (Askitopoulou et al. 2000; Thurmon and Charles 2007).

1.2 Total intravenous anaesthesia

Total intravenous anaesthesia (TIVA) is a technique of general anaesthesia that uses agents given solely by the intravenous route, and in the absence of all inhalational agents (Campbell et al. 2001). Total intravenous anaesthesia is a relatively new method of anaesthesia used in humans and animals that has shown satisfactory results so far. Drugs like propofol and alfaxalone have been used for anaesthesia in veterinary medicine. These drugs are used for induction to allow endotracheal intubation or for maintenance of the anaesthesia (Ferre et al. 2006, Seliskar et al. 2007, Muir et al. 2008).

1.3 Aim of the study

The objective of this study was to investigate the anaesthetic and cardiopulmonary effects of alfaxalone in comparison to propofol when used for TIVA during ovariohysterectomy in dogs. The results may be of value in clarifying effects and dosage regimes of alfaxalone when used for TIVA during surgical stimulation.

This specific aims of this prospective randomised clinical study were to compare:

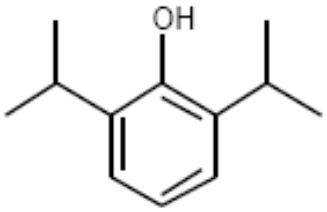
i) anaesthetic effects (induction, maintenance and recovery from anaesthesia)
ii) cardiovascular effects (heart rate, blood pressure, peripheral perfusion)
iii) respiratory effects (respiratory rate, tidal volume, expired carbon dioxide)
iv) effects on arterial blood gas profile

of alfaxalone in comparison to those of propofol at clinically relevant dosages.

Chapter 2

2.1.1 Propofol: chemical and physical characteristics

Propofol is short-acting intravenous anaesthetic agent that belongs to the alkylphenol family (Sebel and Lowdon 1989; Trapani et al. 2000).



Structural and molecular formula of propofol (Trapani et al. 2000).

Propofol is insoluble in water and was therefore initially prepared with Cremophor EL. Propofol was reformulated in an emulsion containing soybean oil (100mg/ml), glycerol (22.5 mg/ml) and egg lecithin (12mg/ml) because of anaphylactic reactions associated with Cremophor EL in the early formulation. In addition, edetate disodium (EDTA) or sodium metabisulfite has been added as a preservative (Marik, P 2004). Propofol supports bacterial growth and endotoxin production because of the formulation as a lipid emulsion (Strachan 2008). Once exposed to air, any propofol remaining in an ampoule, syringe or infusion pump after use for an anaesthetic procedure must be discarded. (Arduino et al. 1991; Strachan 2008).

2.1.2 Pharmacokinetic properties

The pharmacokinetic profile of propofol was evaluated in Greyhounds and mixed-breed dogs (Zoran et al. 1993). Disposition of propofol was adequately described by a 2-compartment open model, with a rapid distribution phase followed by a slower elimination phase. When findings in Greyhounds were compared with those in mixed-breed dogs, significant differences were observed in mean concentrations of propofol in blood, recovery characteristics, and

apparent volume of distribution, volume of distribution at steady state, and total body clearance (Zoran et al. 1993).

Following bolus injections of propofol, blood concentrations decline rapidly (Langley et al. 1988; Gepts et al. 1987). Hepatic metabolism is considered the main elimination pathway of propofol. However; total body clearance of propofol exceeds liver blood flow suggesting an extrahepatic site of metabolism (Langley et al. 1988; Upton et al. 2005; Veroli et al. 1990). Presence of propofol metabolites in urine after a single intravenous bolus dose of propofol before the hepatic phase has been reported (Veroli et al. 1990). In addition, it has been demonstrated that the lungs take part in the biotransformation process of propofol in humans and cats (Dawidowicz et al. 2000; Matot et al. 1993).

A prolonged elimination half life can occur following major operations in humans and may contribute to a delayed awareness. Elderly patients may exhibit reduced clearance that could decrease the maintenance propofol requirement and prolong recovery (Shafer et al. 1988).

2.1.3 Plasma protein binding

More than 98% of propofol is protein-bound in whole blood over a range of clinical concentrations. Both red blood cells and serum proteins (nearly exclusively albumin) equally bind propofol (Mazoit et al. 1999). Propofol binds to albumin 95% and to α-1acid glycoprotein 54% of the time when evaluated in vitro (Garrido et al. 1994). In vivo studies of the pharmacokinetics of propofol in rats, dogs, rabbits and man, showed a high protein binding ability of (96-98%) (Garrido et al. 1994). In addition, there was no apparent change in binding over the concentration range investigated for dog, rat, or human plasma. However over the concentration range used for rabbits, protein-binding decreased gradually from 97.3% to 94.3% (Cockshott et al. 1992). Critically ill patients that had low albumin levels and high α_1-acid-glycoprotein had significantly higher free propofol levels, supporting the idea that potent drugs should be given with great care in these patients (Zamacona et al. 1997).

2.1.4 Distribution

Propofol has a large volume of distribution, fast onset and short, predictable duration of action due to its rapid penetration of the blood-brain barrier and distribution to the CNS, followed

by redistribution to inactive tissue depots such as muscle and fat (Kanto et al. 1989). The distribution of propofol is extensive, with the initial volume of distribution approximating body volume in all species, demonstrating a high affinity of this lipophilic molecule for tissues. Redistribution is also extensive with steady state (V_{SS}) in the rat, dog and rabbit of about 5 – 10 times body weight (Cockshott et al. 1992). Propofol has a distribution half-life of approximately 2 to 4 minutes and a volume of distribution (Vd) of between 209 and 1008L in humans. Propofol follows an open 3-compartment model, being distributed into two distinct tissue compartments (Langley et al. 1988).

2.1.5 Elimination

Hepatic metabolism is considered as the main elimination pathway of propofol. However in humans it has been demonstrated that kidneys play an important role in the elimination of propofol (Takizawa et al. 2005). Some reports suggest that the lungs are involved in the extrahepatic metabolism of propofol in a number of animal species. (Dutta et al. 1998; Kuipers et al. 1999)

2.1.6 Half-life

Elimination half-life evaluated in human patients undergoing general anaesthesia using propofol infusion was 116 +/- 34 minutes. Human patients undergoing major (intra-abdominal) surgery had longer elimination half-life values (136 +/- 40 vs. 108 +/- 29 min) (White 2008). Mean elimination half-life in dogs anaesthetized with a constant rate infusion of propofol was 322.3 minutes (Nolan and Reid 1993). In the same study, all dogs recovered rapidly from anaesthesia despite the duration of the infusion (Nolan and Reid 1993).

2.1.7 Clearance

The liver is probably the main organ involved in the clearance of propofol.
Renal as well as pulmonary clearance has also been shown to be involved. (Dutta et al. 1998; Kanto and Gepts 1989; Kuipers et al.1999; Langley et al. 1988; Zoran et al. 1993). Estimates of total body clearance of propofol vary from 94 to 139 L/h. Total clearance and initial volume of

distribution is reduced in old age as well as patients who have received fentanyl (Langley et al. 1988).

2.1.8 Metabolism

Propofol is mainly metabolised in the liver by glucuronidation resulting in the conjugation of propofol with glucuronic acid (Simons et al. 1998; Vree et al. 1999). Hydroxylation of propofol, catalysed by cytochrome P450 (CYP), accounts for approximately 40% of the dose (Guitton et al. 1998; Simons et al. 1998; Vree et al. 1999). In dogs the major metabolites of propofol are conjugates of 2,6-diisopropyl-1,4-quinol (4-hydroxypropofol) (Simons et al. 1991). Clearance as well as anaesthetic recovery in Greyhounds is significantly slower compared to other breeds of dogs (Robertson et al. 1992; Zoran et al. 1993).

Administration of propofol for an extended period resulted in red blood cell injury and excessive Heinz body formation in cats (Andress et al. 2008; Matthews et al. 2004). The clinical significance of this finding is unknown (Matthews et al. 2004). Increased recovery times, and clinical toxic signs were also observed because of the reduced the ability of cats to conjugate phenol (Andress et al. 2008). No cardiopulmonary differences were detected, and no apparent cumulative effects were observed when metabisulfite propofol was administered (Matthews et al. 2004). Single administration of propofol for induction and maintenance in cats does not cause signs of toxicity (Brearley et al. 2008).

2.2.9 Excretion

Propofol is eliminated primarily in urine (60–95% of the dose). Fecal elimination (13–31% of the dose) occurred in rats and dogs, but was minimal (<2%) for rabbits. Biliary excretion leading to enterohepatic recirculation associated with increased sulphate conjugation occurred in rats and dogs, but not in rabbits, resulting in a marked interspecies variation of drug clearance and metabolite profiles (Simons et al. 1991).

2.2.10 Propofol: Pharmacodynamic properties

Propofol is a short-acting intravenous anaesthetic agent that belongs to the alkylphenol family (Langley and Heel 1988). In dogs and cats it is usually injected slowly as a bolus to enable intubation and initiation of inhalation anaesthesia (Morgan and Legge 1989).The mode of action of propofol involves a positive modulation of the inhibitory function of the neurotransmitter g-aminobutyric acid (GABA) through $GABA_A$ receptors (Trapani et al. 2000).

Sedative concentrations of propofol cause depression of breathing responses to hypercapnia due to an exclusive effect of propofol within the central chemo-reflex loop at the central chemo-receptors (Nieuwenhuijs et al. 2001). This effect can be potentiated by the concurrent use of $alpha_2$-adrenergic agonist or opioids during anaesthesia. Dose reduction and slower speed of administration reduces the degree of depression (Langley and Heel 1988; Sebel and Lowdon 1989; Short and Bufalari 1999; Trapani et al. 2000). Propofol at hypnotic and anaesthetic doses causes significant decreases in heart rate, mean arterial pressure, and left ventricular systolic pressure, while high dosages might cause increases in end-diastolic volume and end-systolic volume, as well as reductions in end-systolic elasticity, indicating a direct negative inotropic effect (Hettrick et al. 1997; Langley and Heel 1988; Sebel and Lowdon 1989; Short and Bufalari 1999).

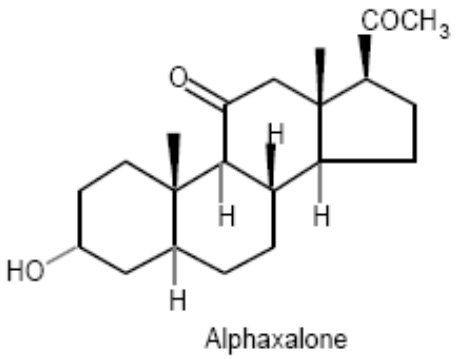
Following a single dose of 6.55 mg/kg for unpremedicated dogs and 4.5 mg/kg for premedicated dogs mean recovery times ranged, depending on the method of anaesthesia, from 23 to 40 minutes (Morgan and Legge 1989). Continuous infusion at a rate of 0.4mg/kg/min for a period of 60 minutes resulted in prolonged recoveries in Greyhounds (Robertson et al. 1992, Zoran et al. 1993). When compared to thiopentone, faster and more coordinated recoveries were achieved with propofol in humans and dogs (Boysen et al. 2008; Quandt et al. 1998). Propofol used for TIVA provided a slower but smoother recovery when compared with propofol-induced and isoflurane-maintained anaesthesia in dogs (Yi-Chin et al. 2007). Propofol is characterised by smooth inductions and short recovery times even when used as a constant rate infusion for maintenance of anaesthesia (Adetunji et al. 2007; Ambros et al. 2008; Matthews et al. 2004; Nolan and Reid 1993; Watkins et al. 1987).

Appropriate muscle relaxation for most surgical procedures is achieved with propofol (Grimm et al. 2001; Duke 1995). Propofol may be a potentially useful drug in the treatment of status epilepticus in patients in whom benzodiazepines, barbiturates and phenytoin have failed failed (Borgeat 1997; De Riu et al. 1992; Lowson et al. 1990).

2.2 Alfaxalone

2.2.1 Chemical and physical characteristics

Alfaxalone (3a-hydroxy-5a-pregnane-11,20-dione) is a synthetic neuroactive steroid which interacts with the gamma aminobutyric acid ($GABA_A$) receptor, producing general anaesthesia and muscle relaxation (Ferre et al. 2006; Glen et al. 1987).



Alfaxalone molecule (Trapani et al. 2000).

Alfaxalone was introduced into the human and veterinary medicine market in 1971 as Althesin® and Saffan® respectively and was composed of both alfaxalone (3-hydroxy-5-pregnane-11,20-dione) and alfadolone acetate [acetoxy-3-hydroxy-5-pregnane-11,20-dione] (Child et al. 1971; Sear 1996). At that time, it had to be compounded with a solubilising agent, CT1341 in 20% polyethoxylated castor oil (cremophor-EL) surfactant, due to its hydrophobicity (Sear 1996). Hypersensitivity reactions related to the use of Cremophor were noted in dogs, cats and humans (Pearson et al. 2003). Histamine release, which was related to cremophor resulted in anaphylactic reactions characterised by hypotension, swollen paws and ears and occasional pulmonary edema in cats (Child et al. 1971; Dodman 1980; Sear 1996; Pearson et al. 2003). A new water soluble formulation (without alfadolone) has been developed for use in small animals by solubilising alfaxalone in 2-hydroxypropyl-beta cyclodextrin (HPCD) instead of cremophor (Ferre et al. 2006; Muir et al. 2008). This formulation has recently been marketed as Alfaxan® [Jurox Pty Ldt, Rutherford, NSW, Australia] (Ferre et al. 2006; Wittem et al. 2008).

2.1.2 Pharmacokinetic properties

The pharmacokinetic profile of alfaxalone after a single intravenous administration has been described in Beagle dogs (Ferre et al. 2006).

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Table 1 Main pharmacokinetic variables estimated by non-compartmental analysis of alfaxalone plasma concentrations after bolus intravenous administration of alfaxalone as Alfaxan-CD RTU in eight healthy Beagle dogs at 2 and 10 mg kg^{-1} BW (mean ± SD; harmonic mean ± SE for $t_{\frac{1}{2}}$)

	Dose					
	2 mg kg^{-1}			10 mg kg^{-1}		
	Total	Female	Male	Total	Female	Male
$AUC_{0-\infty}$ (minute mg L^{-1})	35.5 ± 8.7	32.6 ± 7.7	38.4 ± 9.7	198.0 ± 53.2	185.2 ± 61.1	210.8 ± 49.5
Cl_p (mL $minute^{-1}$ kg^{-1})	59.4 ± 12.9	64.5 ± 13.7	54.3 ± 11.5	52.9 ± 12.8	57.2 ± 15.8	48.5 ± 9.1
MRT (minute)	29.7 ± 9.0	26.9 ± 8.6	32.5 ± 9.8	38.5 ± 9.1	37.8 ± 11.8	39.1 ± 7.4
V_d (L kg^{-1})	2.4 ± 0.9	2.2 ± 0.6	2.5 ± 1.2	2.9 ± 0.4	3.0 ± 0.4	2.8 ± 0.4
$t_{1/2}$ (minute)	24.0 ± 1.9	21.8 ± 4.0	26.7 ± 5.1	37.4 ± 1.6	35.2 ± 5.0	39.8 ± 2.8

AUC, area under the curve; MRT, mean residence time.

Pharmacokinetic properties of alfaxalone include rapid onset of activity, high total body clearance, and liver metabolism elimination. Pharmacokinetic properties of alfaxalone in cats have been illustrated as nonlinear. In nonlinear pharmacokinetics, the drug's effects and persistence are not predictable at different doses (Ferre et al. 2006; Whittem et al. 2008).

2.2.3 Plasma protein binding

Albumins are the main binding site of intravenous anaesthetics. Proteinaemia and albuminaemia variations are related to changes in recovery time (Torri et al. 1980). Althesin® (alfaxalone and alphadolone acetate) interacts with human plasma steroid binding globulins but it is not sufficient to alter the transport of cortisol in humans (Perrot et al. 1985).

2.2.4 Distribution

Alfaxalone is a highly lipid soluble and water insoluble molecule with extensive tissue distribution (Whittem et al. 2008). The average volume of distribution of alfaxalone in dogs is approximately 2 liters/kg (Ferre et al. 2006). Slow intravenous infusion of Althesin® in rats showed uniform alfaxalone distribution in tissues wiht slight localization in the fat and brain levels comparable to plasma concentrations (Pastorino et al. 1979).

2.2.5 Elimination

The main elimination pathway of alfaxalone is considered to be hepatic metabolism. Kidneys and pulmonary metabolism are thought to be involved as well in the elimination of this drug (Ferre et al. 2006; Holly et al. 1981; Sear et al. 1995; Simpson et al. 1978). Following a bolus dosing to surgical patients of alfaxalone-alfadolone, elimination half-life of about 30 minutes was reported in humans (Sear et al. 1995).

2.2.6 Half-life

Following a bolus of 2 and 10 mg/kg of Alfaxan® in different dog groups the average terminal half-life was approximately 30 minutes (Ferre et al. 2006) and was shown to be 37 and 42 minutes respectively in unpremedicated and medicated Greyhounds (Paloske et al. 2009). In cats, administration of 5 and 25 mg/kg of Alfaxan® resulted in a terminal half life of about 45.2 and 76.6 minutes respectively (Whittem et al. 2008).

2.2.7 Clearance

After a bolus of 2 and 10 mg/kg of alfaxalone in dogs, plasma clearance was 59.4 ± 12.9 and 52.9 ± 12.8 ml/kg/min respectively (Ferre et al. 2006). In cats, plasma clearance of alfaxalone given a dose of 5 and 25 mg/kg was 25.1 and 14.8 ml/kg/min respectively (Whittem et al. 2008).

2.2.8 Metabolism

The metabolism of Althesin® (alphaxalone and alphadolone acetate) in humans has been studied. Two metabolites, 20 alpha-reduced alphaxalone and alphadolone, as well as the two parent steroids, have been detected in plasma during and after infusion of Althesin® (Holly et al. 1981; Sear 1996). The effects of Althesin® depend upon the functional condition of the liver (Novelli et al. 1977). In patients with normal renal function alfaxalone is probably taken up by the liver, metabolized to a more polar compound and excreted in the urine. In patients with anuria the length of action is not prolonged (Strunin et al. 1977).

2.2.9 Excretion

Once alfaxalone has been metabolized, it is excreted in the urine. Small amounts may be excreted in the bile (Sear 1996; Strunin et al. 1977).

2.2.10 Alfaxalone: Pharmacodynamic properties

The mechanism of action of alfaxalone in the central nervous system involves stimulation of $GABA_A$ receptors causing an alosteric change that augments GABA mediated chloride ion conductance producing anaesthesia and muscle relaxation (Paul and Purdy 1992; Glen et al. 1987). It has been suggested that the antinociceptive properties of alfaxalone are a result of modulation of GABA or glycine receptors at the dorsal horn of the spinal cord. Additional studies will be required to determine these properties (Ahrens et al. 2008; Gilron and Coderre 1996; Murison et al.2010; Nadeson and Goodchild 2000).

Alfaxalone is characterized by a rapid and smooth induction providing good to excellent short-term anaesthesia in dogs and cats (Ferre et al. 2006; Muir et al. 2008; Muir et al. 2009). Whittem and colleagues studied the pharmacokinetics and pharmacodynamics of alfaxalone after single and multiple intravenous administration at clinical and supraclinical doses in cats. Drug accumulation was not evident. Cardiovascular and respiratory parameters were remarkably stable (Wittem et al. 2008). In a similar study using Alfaxan® (2–5 mg/kg), Muir suggested that the intravenous administration of clinically relevant doses of alfaxalone caused mild vasodilatory effects resulting in minimal changes in heart rate and cardiac output, while larger doses (>15

mg/kg) caused vasodilation and negative inotropic effects with subsequent decreases in arterial blood pressure and cardiac output as well as respiratory depression. A dose of alfaxalone larger than 6 mg/kg caused remarkable respiratory depression and apnea (Muir et al. 2009). Alfaxan® infused at 0.1 mg/kg/min resulted in hypotension (MAP < 60mmHg) and hypoventilation (respiratory rate < 3 breaths/min and $PaCO_2$ > 90mmHg); these were not observed when a lower dose (0.07 mg/kg/min) was utilized that still produced a suitable light plane of anaesthesia (Ambros et al. 2008). Dose-dependent hypoventilation and apnoea were the most prominent side effects observed in dogs anaesthetized with alfaxalone. Anaesthesia in that study was judged to be good to excellent (Muir et al. 2008). A high margin of safety of alfaxalone was also observed in dogs when Alfaxan® was administered intravenously at five times the effective target dose (Schnell et al. 2004 and Ferre et al. 2006). Alfaxalone does not accumulate in tissues after repeated doses because of its rapid metabolism and clearance, and can therefore be used for TIVA (Pasloske et al. 2005). Combination of drugs like α-2 adrenergic agonist and opioids with alfaxalone can reduce the anaesthetic induction dose of alfaxalone (Maddern et al. 2010). Alfaxalone produces short recovery times even when it is used as TIVA. When dogs were anaesthetised using alfaxalone at 0.07 mg/kg/min during 120 minutes, they recovered within 36 to 57 minutes (Ambros et al. 2008). Alfaxalone used at 1 mg/kg in premedicated ponies for castration resulted in a standing position time of 34 ± 9 minutes (Leece et al. 2009). Alfaxalone has been used in dogs producing adequate quality for induction and maintenance of anaesthesia. Variations in cardiopulmonary parameters were observed in relation to the dose and anaesthesia technique utilized.

Chapter 3

3.1 Materials and methods

A total of 14 mixed-breed bitches with a body weight ranging between 16 - 42 kg admitted for elective ovariohysterectomy to the Onderstepoort Veterinary Academic Hospital (OVAH) were included into the study. Only normal healthy dogs based on full physical examination, total hematology, and serum chemistry analysis were included. Dog's ages were between 0.5 and 5 years and they were classified as American Society of Anesthesiology Score 1.

Owner consent for the use of the dogs and institution ethical approval was obtained prior to inclusion of the dogs in the study. Animals were admitted to the OVAH the morning of the surgery. Food was withheld for at least 10 hours before anaesthesia, while water was withheld the morning of the surgery.

All dogs were premedicated with acepromazine hydrochloride (Aceprom, Bayer, Isando, South Africa) at a dose of 0.01 mg/kg and morphine (Morphine Sulphate-Fresenius PF, Port Elizabeth, South Africa) at 0.4mg/kg administered subcutaneously (s/c), about 30 minutes before general anaesthesia. The right cephalic vein was catheterized in all dogs using a 20-gauge catheter (Jelco Smiths Medical International Ltd, Rossendale, Lancashire ,UK) for administration of intravenous fluids (Intramed Ringer Lactate Solution, Fresenius Kabi, Port Elizabeth, South Africa). An additional 20-gauge catheter was placed in the left cephalic vein for constant rate infusion (CRI) of the anaesthetic drugs.

The dogs were randomly assigned according to the order of arrival at the hospital to one of two groups: Group 1, that received propofol (Propofol 2, 6-di-isopropyphenol 1%. Fresenius Kabi, Halfway House, South Africa) and Group 2, that received alfaxalone (Alfaxan CD-RTU, Kyron, Benrose, South Africa) as TIVA.

General anaesthesia was induced with intravenously administered propofol at a dose of 6 mg/kg (Group 1) and alfaxalone at a dose of 2 mg/kg intravenously (Group 2) over a period of about 40 seconds. Both drugs were given to effect until loss of jaw tone and pharyngeal reflex made tracheal intubation possible. The quality of anaesthetic induction was scored in both groups (Table 1). This method of scoring of induction was obtained from a previous study (Muir et al. 2008). Oxygen at 30 ml/kg/min was supplied for the first ten minutes after induction and then at 10 ml/kg/min during the maintenance of the anaesthesia.

After induction, the maintenance of the anaesthesia was done using between 0.3 - 0.5 mg/kg/min of propofol (Group 1) and 0.1 – 0.12 mg/kg/min of alfaxalone (Group 2). A syringe-driving pump (Injectomac MC Agilia, Fresenius Kabi) was used to perform the CRI of the drugs after endotracheal intubation. (Figure 1).

Dogs were maintained in a surgical anaesthesia plane by assessing pedal reflex, palpebral reflex, eyeball position and jaw tone. The variation on cardiorespiratory parameters in response to surgical manipulation was another means used to evaluate the anaesthestic plane. Depth of anaesthesia was assessed every 5 minutes and depending on outcome of the assessment, the dose of either propofol or alfaxalone was adjusted by about 10% or left unchanged to maintain a surgical plane of anaesthesia.

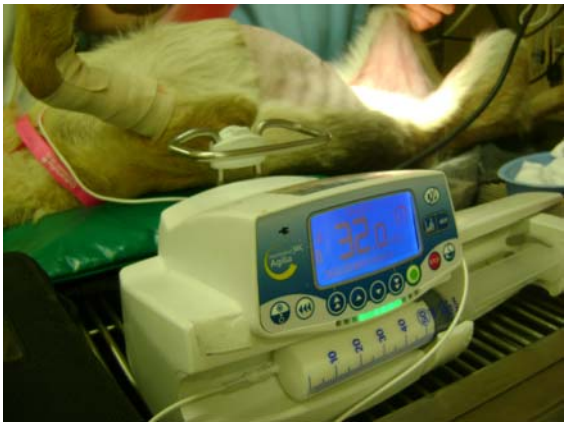

Figure 1 – Anaesthetised dog being prepared for surgery. A CRI of propofol is being administered using syringe-driving pump.

Anaesthetized dogs were allowed to breath spontaneously, however hypercapnia was prevented by the use of ventilatory support depending on end-tidal carbon dioxide concentrations ($ETCO_2$). $ETCO_2$ was maintained between 35 and 55 mmHg for ventilated and spontaneously breathing dogs.

Carprofen 2.2 mg/kg (s/c) (Rimadyl injectable solution. Carprofen 5 %, Pfizer, South Africa). was given for post-operative analgesia. Ringers lactate was administered intravenously to all dogs from the time of induction of general anaesthesia until 2 hours post-operatively at a rate of 10ml/kg/hr.

Ovariohysterectomy was performed after appropriate clipping and surgical preparation of the area using a ventral midline approach. The anaesthetist was warned when stretching and ligation of the suspensory ligaments, pedicles and cervix were done (Figure 2).

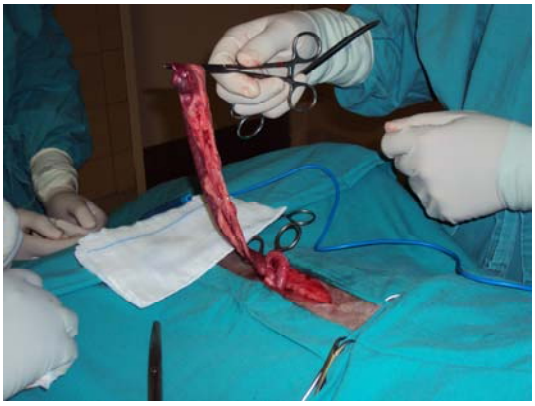

Figure 2 – Ovariohysterectomy using ventral midline approach.

An indwelling 22-gauge arterial catheter (Arrow arterial indwelling catheter 22 Ga, Arrow international, Inc., PA.USA) was placed into the femoral artery 30 minutes after the induction. Anaerobic collection of blood samples for analysis of blood gases, as well as for measurement of arterial blood pressure was done from this catheter. Arterial blood gas samples of 1mL each were taken at 35, 70, 90 minutes after induction and 20 minutes after the end of the anaesthesia (Figure 3).

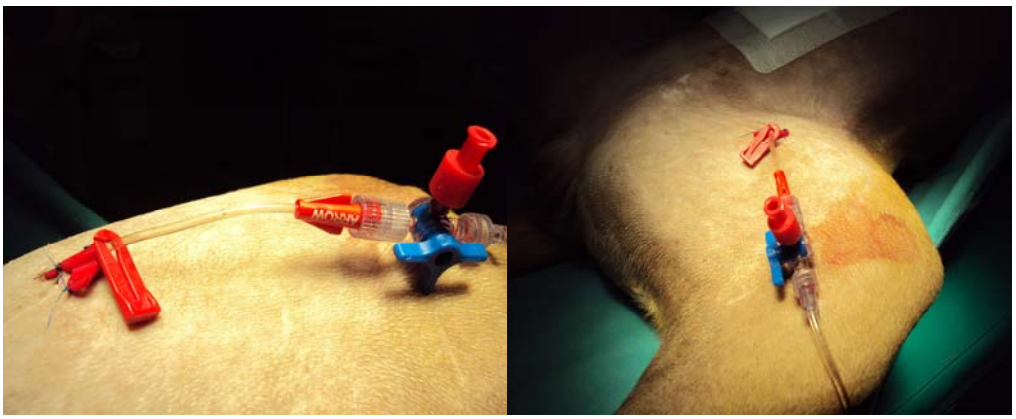

Figure 3 – Femoral artery catheterization.

Monitoring of the patient was done every 5 minutes during the anaesthesia. It included cardiovascular (invasive diastolic (DAP), systolic (SAP) and mean arterial blood pressure (MAP), pulse rate, heart rate and capillary refill time), respiratory (respiratory rate, mucous membrane colour, hemoglobin oxygen saturation, end-tidal CO_2 ($ETCO_2$) and tidal volume (TV), ocular (pupil dilation, palpebral and corneal reflexes and eyeball rotation), musculoskeletal (jaw tone) and nervous system evaluation (anaesthetic plane based on pedal reflex, palpebral reflex, position of the eyeball and responses to surgical manipulation) (Figure 4 - 5).

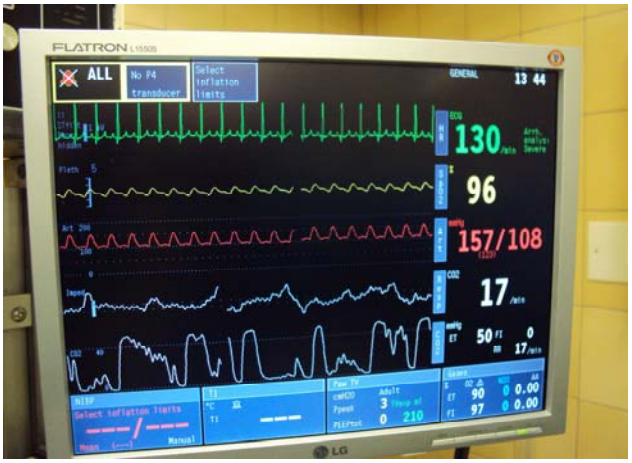

Figure 4 - Monitoring of the anaesthesia during ovariohysterectomy

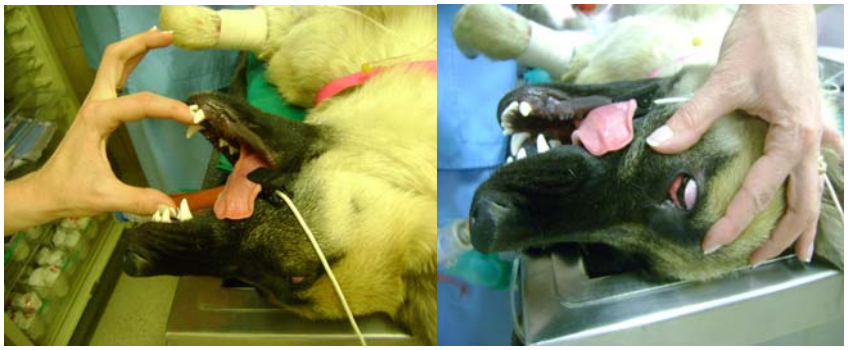

Figure 5 – Evaluation of jaw tone and eye rotation 5 minutes after induction.

Time to extubation, sternal recumbency, standing and voluntary motion were recorded (Table 3). All times were determined as the interval between the time the administration of anaesthesia maintenance drugs by CRI was terminated and the time a particular event occurred (Table 4-5). Quality of recovery from anaesthesia was scored (Table 2).

3.2 Data analysis

Data on age, weight, haematocrit, total serum proteins, albumin, white cell count, induction score, recovery score, time to extubation, time to head-lift, time to sternal position and time to standing position were considered non-parametric and were tested for statistically significant differences between groups using the Mann-Whitney U test. All non-parametric values are presented as median (inter-quartile range).

Repeatedly measured parameters (e.g. heart rate, arterial blood pressure etc) data were analysed for statistically significant differences between and within groups using the analysis of variance (ANOVA) test and values are presented as mean ± deviation. If statistically significant differences were found, a post hoc analysis (Tukey-Kramer pairwise comparison) was conducted to determine differences when compared to the baseline value and between groups at the same time period. For statistical comparison of repeatedly measured data, the readings obtained at the following times were used: before sedation (baseline), 5 minutes after induction, just before first surgical incision, at time of surgical incision, at pulling of right suspensory ligament, at pulling of left suspensory ligament, at cervical ligation and at the end of anaesthesia.

A value of $P < 0.05$ was considered statistically significant.

Chapter 4

4.1 Results

There were no statistically significant differences between groups in terms of median age, weight, preanaesthetic haematology and most of the biochemical parameters. Plasma albumin levels were significantly different between group 1 and 2, even though the measured values were within normal clinical limits.

Adequate degree of sedation was observed in all dogs before induction.
Smooth and rapid induction of the anaesthesia was observed in all dogs. Endotracheal intubation was easily achieved. All dogs lost consciousness in less than 60 seconds. The quality of the induction was scored as 1 (the highest quality in a range of 1 to 3) for all the dogs. Mean induction dose for the propofol and alfaxalone group was 5.8 and 1.9 mg/kg respectively. No excitement or apnea was observed during the induction.

The mean CRI dose rate that was adequate to maintain a surgical anaesthesia plane was 0.37 ± 0.09 and 0.11 ± 0.010 mg/kg/min for propofol and alfaxalone respectively.

Base line values for SAP, MAP, DAP, arterial pH, $PaCO_2$, PaO_2 and bicarbonate were not obtained in this study (Tables 4 - 6) as arterial catheters were only placed after induction of general anaesthesia. Ideally these values should have been recorded; however the cases used in this study were client-owned clinical cases and a prior anaesthesia for arterial catheter placement to collect these values was not possible. Typical base values shown in Tables 7 and 8 were obtained from a similar study using research dogs (Ambros et al. 2008), but these numbers were not included in the statistical analysis. Cardiovascular parameters (HR, SAP, MAP, DAP) did not vary significantly between the two groups during the anaesthesia. However significant changes were observed in SAP, DAP, MAP when data of the same group were compared to the first measured variable (Table 4).

Respiratory rate, $ETCO_2$, TV, arterial pH, $PaCO_2$, PaO_2 and bicarbonate between the two groups did not change significantly during the anaesthesia (Tables 5 and 6). End tidal CO_2 levels measured during the anaesthesia for both groups were more than 45 mmHg but below 55mmHg. Arterial partial pressure of CO_2 was more than 50 mmHg but below 55mmHg in both groups during the anaesthesia. One dog in the alfaxalone group registered remarkable respiratory depression with high $ETCO_2$ (59 mmHg) about sixty minutes after induction. To maintain $ETCO_2$

within normal ranges it was necessary to ventilate this dog. The anaesthetic period in this patient proceeded uneventfully from that point forward.

The maintenance of anaesthesia was characterized by good muscle relaxation and relaxed jaw tone. There were increases in cardiorespiratory parameters after surgical stimulation or when the suspensory ligament was pulled during the surgery; notwithstanding these changes were not pronounced (Tables 4 and 5).

Times to extubation, head lift, sternal recumbency, and standing did not vary significantly between the two groups (Table 3). The quality of the recovery for the propofol group was assessed as excellent (n= 6 dogs) and fair (n = 1 dog). The one dog whose quality of recovery from anaesthesia scored as fair exhibited a prolonged extubation and head-lift time; however the standing time did not differ significantly from the rest. Recovery from alfaxalone was scored as excellent (n = 7 dogs).

Chapter 5

5.1 Discussion

The present study indicates that alfaxalone and propofol produce adequate anaesthetic induction and maintenance for ovariohysterectomy in healthy dogs premedicated with acepromazine and morphine. Cardiopulmonary changes were not pronounced with respiratory depression during the surgery being the most evident adverse effect. Previous studies evaluated the cardiorespiratory effects of alfaxalone used for induction and maintenance of anaesthesia in dogs. These studies demonstrated satisfactory results with fast induction, tolerable cardiorespiratory depression, good muscle relaxation, and uneventful recovery and made conclusions comparable to those of the present study (Ambros et al. 2008; Ferre et al. 2006; Maddern et al. 2010; Muir et al. 2008; Pasloske et al. 2009).

Mean arterial blood pressure did change significantly in the propofol group when the suspensory ligaments were pulled and during ligation of the cervix (Table 4) but this was not observed in the alfaxalone group. Cardiovascular parameters of the propofol group showed significant variation when compared with the baseline values in the present study. One of the hemodynamic effects of propofol is a decrease in arterial blood pressure with accompanying decreases in systemic vascular resistance (Lowe et al. 1996; Langley and Heal 1988; Sebel and Lowdon 1989; Smith et al. 1993). In dogs this effect is thought to be due to alteration of heart contractility causing a negative inotropic effect (Brussel et al. 1989). In humans bradycardia is significantly more common when propofol is combined with opioids or in patients that chronically use beta-adrenergic receptor-blocking drugs (Hug et al. 1993). Our dogs had been premedicated with morphine and this may have contributed to a synergistic effect on heart rate when combined with propofol. The haemodynamic effects of alfaxalone were studied by others who reported mild to moderate decreases in arterial blood pressure after induction in cats and dogs using therapeutic doses (Dyson et al. 1987; Muir et al. 2008; Muir et al. 2009; Pablo et al. 1998). Observed mean heart rate in the alfaxalone group in the present study (mean SD 97.4 ±10.4) is higher than that reported by others (mean SD 84 ± 15) (Jansen and Uilenreef 2009). This difference is likely due to the use of dexmedetomidine used as premedication in the latter study (Jansen and Uilenreef 2009).

The present study suggests that changes in heart rate, SAP, MAP, DAP were not pronounced during anaesthesia in either group. This is consistent with the results observed by

others in dogs premedicated with dexmedetomidine and maintained on alfaxalone as TIVA (Jansen and Uilenreef 2009). The most relevant changes of these variables were registered at the moment of pulling the suspensory ligament; however these measured values were within normal clinical limits.

Respiratory rate was significantly lower when compared with baseline in both groups (Table 5) and it was the most relevant finding of the present study. Respiratory depression in dogs after alfaxalone or propofol induction has been previously described (Grimm et al. 2001; Maddern et al. 2010; Muir et al. 2008; Smith et al. 1993). Dose-dependent respiratory depression was observed when 2 - 6 and 20 mg/kg of alfaxalone were administered to unpremedicated dogs (Muir et al. 2008). Periods of apnoea of about 1 - 3 minutes in duration were reported most commonly with dosages of 6 or 20 mg/kg of alfaxalone. In the present study, in which premedicants were also used, followed by an alfaxalone dose of 1.9 mg/kg and propofol dose of 5.8 mg/kg propofol for induction, apnoea was not observed. Other studies observed apnoea and cyanosis with propofol during the induction in dogs especially after rapid injection (Keegan and Greene 1993; Quandt et al. 1998; Smith et al. 1993). In the present study induction was performed to effect over 40 seconds.

Elevation of $PaCO_2$ and decrease of arterial pH was observed during anaesthesia when compared to the samples obtained 20 minutes after the end of anaesthesia (Table 6). A decrease in arterial pH is consequence of an elevated $PaCO_2$ accompanying acidemia (Hood and Tannen 1998). $PaCO_2$ tension increases and pH decreases after alfaxalone or propofol induction (Muir et al. 2008; Smith et al. 1993). Unfortunately as it was previously mentioned it was not possible to have baseline values for $PaCO_2$ and arterial pH. Significant variations in these two variables were observed between the first samples collected and the ones collected 20 min after anaesthesia (Table 6). In order to compare respiratory parameters between the two drugs, dogs were allowed to breath spontaneously in the present study. In a study using dogs premedicated with medetomidine and maintained with propofol that were breathing spontaneously, similar $PaCO_2$ levels to those on our study were observed (Seliskar et al. 2007). Tidal volume increased at the moment when the suspensory ligaments were pulled during surgery but no variations in $ETCO_2$ levels were observed. Tidal volume did not show significant differences between groups (Table 5). Additional studies will be required to determine the relationship between tidal volume and $ETCO_2$ during TIVA.

Most of the drugs used in dogs as premedicants have a direct effect on the dose of the anaesthetic agent and on the recovery characteristics of the patient (Geel 1991; Maddern et al. 2010; Kodaka et al. 1997, Smith et al. 1993). In the present study acepromazine in combination with morphine was administered thirty minutes before propofol or alfaxalone induction. Acepromazine is a phenothiazine derived drug used in veterinary medicine for its sedative effect. The effect of this drug is mediated primarily by blocking of dopamine receptors in the basal ganglia and limbic system (Lemke 2007). Acepromazine blocks α_1 receptors; as a consequence, hypotension is a common and relevant side effect of this drug (Farver et al. 1986; Jacobson et al.1994; Lemke 2007). Respiration is rarely affected by acepromazine at therapeutic doses (Lemke 2007; Popovic and Mullane 1972). Opioids are drugs commonly used to provide analgesia during surgery in veterinary medicine (Lamont and Mathews 2007). This group of drugs mainly interact with opioid receptors, which are found principally in the central nervous system producing analgesia and sedation (Coop and MacKerel 2002; Lamont and Mathews 2007). Common side effects of these drugs include respiratory depression, vomition, decreased gastrointestinal motility and excitement (Jacobson et al. 1994; Lamont and Mathews 2007; Monteiro et al.2009; Wunsch et al. 2009), although sedation is also featured. Morphine is generally used as a primary analgesic in small animal practice (Wanger 2002). As most opiods, morphine produces dose dependent depression of the ventilatory response to increasing $PaCO_2$ levels (Hug et al. 1981; Stein and Rosow 2004; Wanger 2002). Cardiovascular effects of morphine are minimal. Bradycardia is a common effect after morphine injection; however cardiac contractility is minimally affected (Lamont and Mathews 2007; Stein and Rosow 2004; Wanger 2002). In our preliminary trials dogs premedicated with acepromazine at a dose of 0.05 mg/kg and morphine at a dose of 0.2 mg/kg had a prolonged recovery. In addition, a relevant increase in cardiovascular parameters after surgical stimulation was observed. We speculated that acepromazine may have caused hypotension that may have resulted in prolonged recovery. Acepromazine effects on recovery seem to be potentiated by the combination with opioids (Bufalari et al. 1997; Cornick and Hartsfield 1992). Due to this fact, it was decided to decrease the dose of acepromazine to 0.01mg/kg. Increases in cardiovascular parameters during surgery can result from insufficient analgesia, therefore we decided to increase the dose of morphine used in our study to 0.4 mg/kg.

Previous studies using propofol or alfaxalone during TIVA concluded that one of the main problems of these drugs is respiratory depression (Ambros et al. 2008; Jansen and Uilenreef

2009; Hughes and Nolan 1999; Beths et al. 2009). This respiratory depression is attributed to the constant rate infusion of the anaesthetic and ventilatory support was suggested to maintain normocapnia during the anaesthesia (Ambros et al. 2008; Jansen and Uilenreef 2009; Hughes and Nolan 1999; Beths et al. 2009; Smith and White 1991). Higher doses of morphine would have the benefit of reducing the induction and maintenance dose of the anaesthetic agent, but at the same time have negative effects on the respiration. The reduction of the dose of the anaesthetic agent during TIVA may improve respiration. Additional studies will be necessary to demonstrate if increasing or decreasing the dose of morphine or the use of other opioids can improve respiration during TIVA. In the present study measured values of $PaCO_2$ and $ETCO_2$ in both groups during TIVA with spontaneous breathing were elevated. From these observations, it might be inferred that for TIVA with alfaxalone or propofol when used in conjunction with premedication agents (morphine 0.4mg/kg and acepromazine 0.01 mg/kg) during ovariohysterectomy in dogs, ventilatory support might be required to prevent hypercapnia.

The quality of the recovery in the present study was judged to be good to excellent, and all dogs were standing at 74 minutes (69min - 76.5min; inter quartile ratio 1 and 3) and 90 minutes (85min -107min) for propofol and alfaxalone respectively. There was one dog in the propofol group that had a prolonged extubation and head lift time even though the standing time for this dog did not change significantly compared with all dogs. We could not determine the cause of a prolonged extubation. This delayed recovery from anaesthesia could be attributed to the age of the patient (5 years), considering that it was the oldest of all dogs. Recent and previous studies have observed excitement, myoclonus, and prolonged recoveries with alfaxalone in horses, dogs and cats (Beths et al. 2009; Ferre et al. 2006; Goodwin et al. 2009; Sear 1996). In a previous study in which clinical and supra-clinical doses of Alfaxan® were used for induction in dogs, agitation and noise hypersensitivity were reported in a small number of involved dogs (Ferre et al. 2006). In the present study dogs were recovered in a quiet and warm place with normal recorded temperatures and they did not receive any type of stimulus until the complete recovery was finished. No signs of excitement or agitation were observed. It should be mentioned that in the study by Ferre et al. (2006) dogs did not received any premedication while dogs in the present were premedicated with acepromazine and morphine.

There were no significant differences in extubation time, head lift time, sternal recumbency time and standing time between the two groups. Despite the fact that all the measured aspects of recovery were more prolonged in the alfaxalone group (Table 3), the

variations between groups were not pronounced. In a study in which premedicated dogs were induced with alfaxalone and maintained with alfaxalone at 0.07 mg/kg/min for 120 minutes, mean extubation time, head lift, sternal recumbency and standing time for were 14, 35, 43 and 52 minutes respectively (Ambros et al. 2008). Measured median intervals for extubation time, head lift, sternal recumbency and standing time in the present study were 20, 32, 60 and 90 minutes respectively, and are higher than those of the Ambros study. One possible explanation is the difference in the mean dose of alfaxalone required for maintenance. In our study 0.11 mg/kg/min was used in comparison with the 0.07 mg/kg/min used in Ambro's study. The reason for this difference is attributed to a deeper anaesthesia plane needed in our study to allow ovariohysterectomy while no surgical stimulus was used in the Ambros study (Ambros et al. 2008).

In conclusion, alfaxalone used as TIVA in premedicated dogs produced anaesthesia of the same quality as that produced by propofol during ovariohysterectomy. Smooth and rapid induction without complication was observed with both anaesthetic agents. Cardiopulmonary effects were similar for both propofol and alfaxalone. Hypoventilation was the most prominent adverse effect from both anaesthetic agents suggesting a need for ventilatory support during prolonged periods TIVA with either anaesthetic agent.

Chapter 6

6.1 Tables

Table 1. System used to score quality of induction of general anaesthesia.

Induction Characteristics	Score
No outward sign of excitement, rapidly assumes lateral recumbency, good muscular relaxation, easily intubated within 60 seconds of finishing dosing.	1
Mild signs of excitement, some struggling, may or may not be intubated within 60 seconds of finishing dosing.	2
Hyperkinesis, obvious signs of excitement, vocalization, defecation or urination, cannot be intubated.	3

Table 2. System used to score quality of recovery of general anaesthesia.

Recovery Characteristics	Score
Assumes sternal recumbency with little or no struggling, and attempts to stand and walk with little or no difficulty	1
Some struggling, requires assistance to sternal recumbency or standing, responsive to external stimuli, becomes quiet in sternal recumbency	2
Prolonged struggling, unable to assume sternal recumbency or difficulty in maintaining sternal or standing position, becomes hyperkinetic when assisted, prolonged paddling and swimming motion	3

Table 3. Recovery time [median (IQR1 – IQR3)] values (minutes) observed after TIVA with alfaxalone and propofol during ovariohysterectomy in dogs.

Variable	Propofol	Alfaxalone
Extubation	19 (8 - 25)	20 (11 - 22)
Head lift	27 (20 - 44.5)	32 (29 - 40)
Sternal recumbecy	45 (33 - 69)	60 (46 - 61)
Standing	74 (69 - 76.5)	90 (85 - 107)

Table 4. Cardiovascular parameters (mean ± SD) in 14 crossbred dogs measured at various intervals after initiation of CRIs of alfaxalone or propofol during ovariohysterectomy in dogs.

Variable	Baseline	5' after induction	Before surgical incision	Surgical incision	Pulling right suspensory ligament	Pulling left suspensory ligament	Cervix ligation	End of anaesthesia
Heart rate (beats/min)								
Propofol	108.2 ± 18.3	99.2 ± 19.5	113.4 ± 27.5	118.7 ± 24.7	127.8 ± 14.15	119.7 ± 19.7	129.4 ± 21.5	131.1 ± 22.7
Alfaxalone	141.1 ± 32.4	139.1 ± 34.2	139.5 ± 17.1	141 ± 16.6	147.1 ± 29.6	146.1 ± 26.6	143.5 ± 25.5	143.7 ± 5.5
SAP (mmHg)								
Propofol			95.7 ± 14.4	99.2 ± 12	124.7 ± 24.4	134.7 ± 20*	145.4 ± 26.8*	130 ± 23.1*
Alfaxalone			96.4 ± 7.8	113.5 ± 22.4	128 ± 21.3*	136 ± 18.9*	134.5 ± 16.8*	128.8 ± 20.3*
MAP (mmHg)								
Propofol			74.2 ± 10.3	74.7 ± 6.1	98.7 ± 17.4	106.7 ± 17*	109.8 ± 22.2*	97.5 ± 13.2
Alfaxalone			79.1 ± 9.7	92.2 ± 18.6	98.7 ± 22.4	103.4 ± 16.3	103.1 ±13.7	108.1 ± 14.5*
DAP (mmHg)								
Propofol			55.7 ± 6.4	61.4 ± 7.8	84.7 ± 15.8	92.5 ± 14.9	92.1 ± 211	84.2 ± 9.2
Alfaxalone			66.2 ± 15.9	78.1 ± 17.3	88.2 ± 25.7	90.2 ± 17.1	89.5 ± 17.7	92.1 ± 12.66

*Significantly ($P < 0.05$) different from first variable measured.

Table 5. Respiratory variables (mean ± SD) in 14 crossbred dogs measured at various intervals after initiation of CRIs of alfaxalone or propofol during ovariohysterectomy in dogs.

Variable	Baseline	5' after induction	Before surgical incision	Surgical incision	Pulling right suspensory ligament	Pulling left suspensory ligament	Cervix ligation	End of anaesthesia
Respiratory rate (breaths/min)								
Propofol	18.2 ± 6	14.5 ± 7.5*	11.8 ± 7.1*	13.1 ± 8*	13.4 ± 3.9*	12.8 ± 4.5*	12.2 ± 4*	14.4 ± 5.8*
Alfaxalone	17.7 ± 9.1	16.8 ± 10.1	9.5 ± 4.5*	10.2 ± 3*	11 ± 3.4*	12.2 ± 2.9*	10.4 ± 2.9*	13 ± 3.6*
End tidal co2 (mmHg)								
Propofol			46 ± 4.8	43.2 ± 10.7	41 ± 7.3	47.2 ± 5.9	46.1 ± 5.8	46.8 ± 4
Alfaxalone			50 ± 6.2	49.7 ± 7.6	50 ± 4.9	46.8 ± 1.8	48.7 ± 4.1	43.7 ± 5.4
Tidal volume (ml/kg)								
Propofol			11.3 ± 5.7	11.9 ± 6.2	12.7 ± 6.4	12.6 ± 7.2	14.2 ± 7.5	13.25 ± 5.5
Alfaxalone			12.4 ± 4.1	11.4 ± 3.7	13.1 ± 4.5	12.5 ± 3.6	13.8 ± 2.8	14.4 ± 4.7

*Significantly ($P < 0.05$) different from baseline measured.

Table 6. Blood gas parameters (mean ± SD) measured at various intervals after initiation of CRIs of alfaxalone or propofol during ovariohysterectomy in dogs.

	Time after induction of anaesthesia (min)			Time after end of anaesthesia (min)
Variable	35	70	90	20
Arterial pH				
Propofol	7.2 ± 0.06	7.2 ± 0.05	7.24 ± 0.02	7.36 ± 0.01*
Alfaxalone	7.25 ± 0.03	7.23 ± 0.06	7.29 ± 0.02	7.36 ± 0.03*
$PaCo_2$ (mmHg)				
Propofol	53.3 ± 6.9	55.2 ± 8.4	50.1± 4.9	37.3 ± 4.1*
Alfaxalone	54.4 ± 7.3	59.3 ± 9.9	52.8 ± 7.3	43.5 ± 4.5*
$Pa0_2$ (mmHg)				
Propofol	299.9 ± 62.6	290.6 ± 112.3	312.3 ± 56.3	74.7 ± 8.1*
Alfaxalone	393.9 ± 78.5	436.5 ± 82.8	442.5 ± 97.8	80.4 ± 12.6*
Bicarbonate (mmol/L)				
Propofol	19.7 ± 1.2	19.4 ± 1	19.8 ± 1.2	21 ± 0.8
Alfaxalone	20.9 ± 0.7	21.5 ± 1.3	22.7 ± 2.5	23.2 ± 1.3

*Significantly ($P < 0.05$) different from first variable measured.

Table 7. Mean ± SD baseline values obtained from a similar study (Ambros et al. 2008).

Variable	Baseline
SAP (mmHg)	
Propofol	119 ± 9
Alfaxalone	117 ± 9
MAP (mmHg)	
Propofol	76 ± 8
Alfaxalone	76 ± 7
DAP (mmHg)	
Propofol	61 ± 8
Alfaxalone	59 ± 9

Table 8. Mean ± SD baseline values obtained from a similar study (Ambros et al. 2008).

Variable	Base line
Arterial pH	
Propofol	7.36 ± 0.02
Alfaxalone	7.35 ± 0.01
$PaCo_2$ (mmHg)	
Propofol	44.4 ± 5.3
Alfaxalone	45.7 ± 6.1
$Pa0_2$ (mmHg)	
Propofol	99 ± 23
Alfaxalone	89 ± 9
Bicarbonate (mmol/L)	
Propofol	24.2 ± 2.6
Alfaxalone	24.4 ± 3.9

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