A Comparison of the Incidence of Apnoea Following Induction of Anaesthesia with Propofol or Alfaxalone in Dogs

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ABSTRACT

Animals are often given combinations of drugs that produce sedation prior to the use of agents that induce general anaesthesia. Following sedation, induction of general anaesthesia can cause a period of apnoea (cessation of ventilation) which is commonly referred to as post-induction apnoea. If post-induction apnoea persists it can pose significant risk to animals undergoing anaesthesia.

This thesis examines the effect of intramuscular premedication drugs acepromazine and dexmedetomidine combined with methadone, commonly used to produce sedation in canines prior to anaesthesia, and the effect of the anaesthetic induction drugs propofol and alfaxalalone on the incidence and duration of post-induction apnoea in healthy dogs. In addition, the effect of the rate of administration of propofol and alfaxalalone on the incidence and duration of post-induction apnoea in healthy dogs is also described.

Prospective, randomised clinical trials identified no difference in effect of the premedication drugs acepromazine and dexmedetomidine on post-induction apnoea when using propofol or alfaxalalone. The results of the trials conducted also did not identify a difference in incidence or duration of post-induction apnoea following either propofol or alfaxalalone; however, a significant effect of rate of administration of these drugs on incidence and duration of post-induction apnoea was detected. The duration of apnoea following propofol or alfaxalalone was significantly longer when these drugs were given rapidly. Based on these findings, propofol and alfaxalalone cause significant post-induction apnoea and the rate of administration of both drugs should be reduced where possible. The incidence and duration of apnoea does not appear to be influenced by the use of acepromazine or dexmedetomidine in combination with methadone for premedication. Monitoring of respiration is recommended when using these premedication and induction agent combinations.
DECLARATION

This is to certify that

(i) this thesis is comprised solely of my original work towards the Master of Veterinary Science except where indicated in the Preface;

(ii) due acknowledgement has been made in the text to all the material used;

(iii) the thesis is 28405 words in length, excluding tables, figures, bibliographies and appendices.
PREFACE

Chapters 3 and 4 of this thesis have been published in the journal *Veterinary Anaesthesia and Analgesia*. In both chapters the candidate was responsible for ≥ 90% of the authorship and the co-authors contributed to experimental design, data collection and editing. All authors have given permission for these publications to be included in this thesis.

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<td>Alpha-1</td>
</tr>
<tr>
<td>α2</td>
<td>Alpha-2</td>
</tr>
<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CO₂</td>
<td>Carbon dioxide</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>ETT</td>
<td>Endotracheal tube</td>
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<tr>
<td>fᵣ</td>
<td>Respiratory frequency</td>
</tr>
<tr>
<td>FRC</td>
<td>Functional residual capacity</td>
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<tr>
<td>GABA</td>
<td>Gamma aminobutyric acid</td>
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<tr>
<td>HR</td>
<td>Heart rate</td>
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<tr>
<td>IM</td>
<td>Intramuscular/intramuscularly</td>
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<td>IPPV</td>
<td>Intermittent positive pressure ventilation</td>
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<td>MA+P</td>
<td>Methadone, acepromazine and propofol</td>
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<tr>
<td>MAC</td>
<td>Minimum alveolar concentration</td>
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<tr>
<td>MV</td>
<td>Manual ventilation</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
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<tr>
<td>O₂</td>
<td>Oxygen</td>
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<tr>
<td>PₐO₂-PₐO₂</td>
<td>Alveolar-arterial oxygen gradient</td>
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<td>PₐCO₂</td>
<td>Partial pressure of arterial carbon dioxide</td>
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<td>PₐO₂</td>
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<tr>
<td>PₑₐCO₂</td>
<td>End tidal carbon dioxide</td>
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<tr>
<td>SaO₂</td>
<td>Haemoglobin oxygen saturation</td>
</tr>
<tr>
<td>SAP</td>
<td>Systolic arterial pressure</td>
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<tr>
<td>SC</td>
<td>Subcutaneous/subcutaneously</td>
</tr>
<tr>
<td>SpO₂</td>
<td>Peripheral oxygen haemoglobin saturation estimated by pulse oximetry</td>
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<tr>
<td>TCI</td>
<td>Target controlled infusion</td>
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Chapter 1: Introduction

Apnoea is defined as the cessation of ventilation and is a common respiratory complication observed during general anaesthesia. Apnoea is a serious adverse event and can cause hypoxaemia (low oxygen \(O_2\) concentration in blood), hypercapnia (high carbon dioxide \(CO_2\) in blood), respiratory acidosis (low blood pH of respiratory origin), atelectasis (collapse of alveoli), and the loss of the respiratory route of administration and removal of gaseous anaesthetic agents (McCaion and Hardman, 2007; Keates and Whittem, 2012). If apnoea is undetected and persists without treatment death can result.

Apnoea following induction of anaesthesia is commonly referred to as post-induction apnoea. In one study looking at causes of anaesthetic mortality, the overall incidence of post-induction apnoea in dogs of varying American Society of Anesthesiologists (ASA) physical status categories was reported as 8.3% (Redondo et al., 2007). While this study did not specifically identify a link between post-induction apnoea and perianaesthetic mortality in dogs, in humans, poor ventilation management (such as undetected oesophageal intubation with apnoea) has been associated with direct anaesthesia-related deaths (Arbous et al., 2001; McCaion and Hardman, 2007). In veterinary anaesthesia, the level of staff knowledge, training and expertise, and the availability of anaesthetic monitoring equipment influence the ability to detect and correct errors in ventilation management. In general veterinary practices, the inconsistent availability of anaesthetic monitoring equipment, the limited advanced training in anaesthesia cause veterinarians to frequently rely on information provided by drug manufacturers to assess the utility of a particular drug for day-to-day anaesthesia. It is therefore important that studies that evaluate drugs used for veterinary anaesthesia are conducted in a manner that reflects typical practice, such as using sedation prior to the
administration of an induction agent, as this can impact the information obtained regarding drug effects.

Propofol (a phenol compound) and alfaxalone (a neuroactive steroid) are intravenous anaesthetic agents that interact with the gamma aminobutyric acid (GABA) A receptor to enhance the inhibitory action of endogenous GABA neurotransmitter and are commonly used in small animal anaesthesia (Amengual et al., 2013). Both agents are characterised by rapid and smooth induction of general anaesthesia (Maney et al., 2013) and by dose-dependent cardiorespiratory depressive properties (Muir and Gadawski, 1998; Muir et al., 2009). Post-induction apnoea following administration of propofol has been well-documented in both human (Briggs and White, 1985; Rolly and Versichelen, 1985; Hannallah et al., 1991; Stokes and Hutton, 1991) and animal studies (Taylor et al., 1986; Muir and Gadawski, 1998; Muir et al., 2009; Amengual et al., 2013). The incidence of post-induction apnoea following the administration of alfaxalone in dogs is less clear with some studies indicating little to no post-induction apnoea, while others suggest a similar incidence to that observed with propofol (Ambros et al., 2008; Muir et al., 2009; Martinez Taboada and Murison, 2010; Keates and Whitterm, 2012; Amengual et al., 2013; Maney et al., 2013). Differences in study methodology and even the definition of post-induction apnoea make direct comparison of the numerous research articles evaluating the use of propofol and alfaxalone in dogs difficult.

Acepromazine and dexmedetomidine are frequently used to provide tranquilization or sedation in dogs. Acepromazine is a phenothiazine compound that exerts anti-dopaminergic effects in the central nervous system leading to sedation, while dexmedetomidine is an alpha-2 (α2)-adrenergic receptor agonist and causes sedation primarily by binding to α2-receptors in the central nervous system (Correa-Sales et al., 1992). Methadone is a pure µ opioid receptor agonist used for analgesia and sedation in dogs and is frequently administered in combination with either acepromazine or dexmedetomidine prior to induction of general
anaesthesia for routine surgical procedures such as neutering. Dexmedetomidine and methadone, when administered alone or in combination, can cause depression of ventilatory drive (Canfrán et al., 2016), whereas acepromazine alone typically has little or no effect on respiration (Popovic et al., 1972). The effect of the combination of sedatives and induction agent on respiratory variables in dogs has not been directly examined.

1.1 Objectives of the Thesis

This thesis will evaluate the current understanding of the respiratory effects of propofol and alfaxalone when used as a general anaesthetic induction agent in dogs. The effect of the use of the sedatives acepromazine and dexmedetomidine before induction of general anaesthesia on respiratory variables will also be examined. The objectives of this thesis are to determine the incidence and duration of post-induction apnoea in healthy dogs following sedation with either a combination of acepromazine and methadone or dexmedetomidine and methadone and induction of anaesthesia with propofol or alfaxalone. A secondary objective of this work is to identify if the rate of administration of propofol or alfaxalone for induction of anaesthesia following dexmedetomidine and methadone premedication influences the incidence and duration of post-induction apnoea in healthy dogs.
1.2 Thesis hypotheses

1.2.1 Study 1: Effect of Premedication Combination

**Hypothesis 1**: The incidence and/or duration of post-induction apnoea will be lower in dogs receiving alfaxalone compared to propofol after premedication with either acepromazine and methadone or dexmedetomidine and methadone.

**Hypothesis 2**: Dogs premedicated with dexmedetomidine and methadone will have a lower incidence and/or duration of post-induction apnoea than dogs treated with acepromazine and methadone.

1.2.2 Study 2: Effect of Rate of Administration of Alfaxalone and Propofol

**Hypothesis 1**: The total induction dose of drug required will be higher when propofol or alfaxalone are administered at a slower rate of administration.

**Hypothesis 2**: The incidence and/or duration of post-induction apnoea is not related to the total induction dose of alfaxalone or propofol.
Chapter 2: Literature Review

2.1 The Respiratory Effects of Acepromazine

Acepromazine is one of the most frequently used sedative drugs in both small and large animal anaesthesia. Belonging to the phenothiazine class of drugs, acepromazine produces sedation through blockade of D$_2$ dopamine receptors. Dopamine receptors are G-protein coupled receptors that are present both pre- and post-synaptically in the central nervous system (Rankin, 2015). Inhibition of the binding of dopamine to these receptors results in a decrease in cyclic adenosine monophosphate (cAMP), adenylate cyclase activity, and altered conduction of calcium and potassium (Lachowicz and Sibley, 1997). It is possible that acepromazine also causes sedation via inhibition of alpha-1 ($\alpha_1$) adrenergic, muscarinic, serotonergic and histaminergic receptors although the precise mechanisms of action have not been determined (Rankin, 2015). Acepromazine provides mild to moderate sedation with good muscle relaxation when administered parenterally at clinical doses of up to 0.05 mg kg$^{-1}$. Adverse effects typically associated with the use of acepromazine are dose-dependent haemodynamic changes due to inhibition of $\alpha_1$-adrenergic receptors such as reduced systemic vascular resistance, cardiac output and arterial blood pressure (Popovic et al., 1972; Coulter et al., 1981; Jacobson et al., 1994).

Popovich et al. (1972) demonstrated that acepromazine given intramuscularly (IM) at a dose of 1 mg kg$^{-1}$ to healthy dogs caused a significant decrease in respiratory rate from baseline values 15 minutes after administration that persisted until 210 minutes after drug administration (the end of the experiment). Despite this reduction in respiratory rate, the study did not identify significant changes in arterial partial pressure of carbon dioxide (PaCO$_2$) or oxygen (PaO$_2$), pH, or haemoglobin oxygen saturation (SaO$_2$). Popovic et al.
concluded that acepromazine at 1 mg kg\(^{-1}\) did not cause an overall disturbance to the respiratory control system as there were no changes in arterial (and therefore alveolar) PaCO\(_2\). It was hypothesised in this study that the decrease in respiratory rate was compensated for by an increased tidal volume as the dogs in the study were observed to have deep respiratory movement. This theory was confirmed in horses administered acepromazine intravenously (IV) prior to hypoxic and hypercapnic ventilatory response tests in a study by Muir and Hamlin (1975). In this study horses had a significant decrease in respiratory rate following administration of acepromazine at all levels of CO\(_2\) inspired, and also at all inspired levels of O\(_2\) less than 21%. There was a corresponding increase in tidal volume in all horses until the inspired CO\(_2\) exceeded 6% when tidal volume decreased.

The respiratory effects of acepromazine (among other sedative agents) were studied in dogs again by Turner et al. (1974). In this study dogs were administered 0.11 mg kg\(^{-1}\) acepromazine IV and various cardiorespiratory variables including mixed expired CO\(_2\), minute volume, respiratory rate (\(f_R\)), arterial pH, PaCO\(_2\) and PaO\(_2\) were obtained. To collect minute respiratory volume data, dogs were trained to lie in lateral recumbency and accept placement of an air-tight face mask connected to a spirometer, micro-catheter sample cell gas analyser and Douglas bag to collect expired gases. Tidal volume was calculated from minute volume and respiratory rate. Turner et al. (1974) found no statistical difference in the arterial oxygen or carbon dioxide tension and minute volume, although they did report a trend towards decreased respiratory rate and minute volume. The authors surmised the lack of increase in PaCO\(_2\) was due to reduced production during the study period. One drawback from the method used to obtain respiratory volume data is the effect of fitting a tight face mask on dogs. Despite training the dogs used in the study to accept the face mask, the authors acknowledged it was possible some apprehension was still present during the procedures which may have influenced results. It would however be difficult to completely overcome
this limitation in any respiratory study in awake dogs. The Turner study appears to confirm the results from Popovic et al., (1972), in that any respiratory changes in normal dogs caused by acepromazine are mild and/or compensated for by changes in tidal volume.

The sedative effects of acepromazine alone and in combination with buprenorphine (a partial μ opioid receptor agonist) or pethidine (a pure μ opioid agonist) were evaluated in 1986 by Taylor and Herrtage. In this study, dogs of various breeds undergoing screening radiography assessment for hip dysplasia were administered acepromazine at 0.13 mg kg⁻¹ IM or acepromazine at 0.07 mg kg⁻¹ combined with buprenorphine 0.009 mg kg⁻¹, or acepromazine 0.07 mg kg⁻¹ combined with pethidine 3.3 mg kg⁻¹ IM. Sedation quality was scored and a single arterial blood sample was analysed for arterial pH, PaCO₂ and PaO₂. No volumetric ventilation measurements were made (such as minute volume or tidal volume) and no baseline arterial blood samples were collected to compare the effects of the combinations of drugs administered. However, a significantly lower arterial pH was noted in dogs receiving either combination of opioid and acepromazine compared to acepromazine alone. PaCO₂ was also significantly higher in dogs receiving acepromazine and an opioid compared to the dogs receiving acepromazine alone, although it is important to note that the mean PaCO₂ of dogs in both combination drug groups were still within normal limits (Taylor and Herrtage, 1986).

The synergistic effect of acepromazine with an opioid drug was demonstrated again in dogs in three studies, one evaluating the cardiorespiratory effects of acepromazine with butorphanol (a κ opioid agonist with partial μ agonist- μ antagonist action) or oxymorphone (a pure μ opioid agonist) (Cornick and Hartsfield, 1992), one that compared IV administration of 0.05 mg kg⁻¹ acepromazine or 0.3 mg kg⁻¹ midazolam combined with 0.01 mg kg⁻¹ buprenorphine or 0.1 mg kg⁻¹ oxymorphone (Jacobson et al., 1994) and one that
compared the effect of acepromazine with three different doses of methadone (a pure \( \mu \) opioid agonist) (Bitti et al., 2017). Cornick and Hartsfield (1992) reported a significant decrease in respiratory rate over time with 0.22 mg kg\(^{-1}\) acepromazine and 0.22 mg kg\(^{-1}\) butorphanol administered either IM or IV and 0.22 mg kg\(^{-1}\) acepromazine IV and 0.22 mg kg\(^{-1}\) oxymorphone IV combinations. This study also found a general trend towards increasing PaCO\(_2\) and decreasing PaO\(_2\) and pH over time in all groups, but these changes were not statistically significant. The results reported by Jacobson et al., (1994) were variable but suggestive of a general decrease in minute volume indexed to body weight in dogs given acepromazine compared to midazolam, although significance was only demonstrated in dogs receiving buprenorphine. There was however, a significant decrease in arterial pH and increase in PaCO\(_2\) in dogs receiving acepromazine and oxymorphone and there was a significant decrease in PaO\(_2\). In contrast, no significant changes in PaCO\(_2\) or PaO\(_2\) were observed in dogs receiving acepromazine and buprenorphine, although minute volume indexed to body weight did decrease in this group. The results from the study by Bitti et al., (2017) found no significant changes in PaCO\(_2\) or PaO\(_2\) after 0.05 mg kg\(^{-1}\) acepromazine IM administration, however the administration of methadone at all doses tested (0.25 mg kg\(^{-1}\), 0.50 mg kg\(^{-1}\), and 0.75 mg kg\(^{-1}\) IM) with acepromazine produced mild respiratory acidosis (the lowest mean pH being 7.300\(\pm\)0.072 in dogs receiving the highest dose of methadone with acepromazine). These results suggest that acepromazine alone has minimal effects on respiration in healthy dogs, but when combined with an opioid for sedation there may be more profound effects on ventilation.

In 1995, Stepiesn et al. reported the cardiorespiratory effects of acepromazine and buprenorphine in awake healthy dogs. In this study, dogs were administered 0.1 mg kg\(^{-1}\) acepromazine IV after baseline haemodynamic and respiratory values were recorded, 15 minutes later dogs were then also given 0.005 mg kg\(^{-1}\) buprenorphine IV. After a further 15
minutes a second dose of 0.005 mg kg⁻¹ or 0.09 mg kg⁻¹ buprenorphine was administered IV. Stepien et al., (1995) showed the respiratory rate decreased in all dogs after administration of acepromazine (before administration of buprenorphine), but the arterial and venous blood gas values (arterial and venous pH, PaCO₂, PaCO₂, venous partial pressure of CO₂ (PvCO₂) and venous partial pressure of oxygen (PvO₂) and arterial and venous bicarbonate) did not change in this time. The authors concluded (similar to Popovic et al., (1972)) there was likely an increase in tidal volume to maintain adequate alveolar ventilation, although the authors went further than Popovich et al., (1972) in proposing that the change in respiratory rate was more likely due to sedation and reduced anxiety rather than due to direct effects of acepromazine on respiratory centres in the brain or as compensatory mechanisms to changes in acid-base status in dogs in the study. As with other studies evaluating acepromazine administration with buprenorphine in healthy dogs, the study by Stepien et al., (1995) demonstrated an increase in PaCO₂ following administration of buprenorphine in addition to acepromazine with a concurrent decrease in pH, however the authors noted no additional changes at the highest dose of buprenorphine and suggested there may be a ‘ceiling effect’ on respiratory depression with high doses of buprenorphine.

The results of the studies by Popovic et al., (1972); Turner et al., (1974); Taylor and Hertrage, (1986); Cornick and Hartsfield, (1992); Stepien et al., (1995) and Muir and Hamlin, (1975) suggest that acepromazine has minimal effect on overall pulmonary function in unanaesthetised animals, as decreases in respiratory rate are compensated for by an increase in tidal volume. However, the addition of an opioid class drug appears to alter the respiratory effects of acepromazine and the opioid administered and, in most cases, cause some degree of respiratory depression as evidenced by decreases in arterial pH with an increase in PaCO₂.
In contrast to the studies discussed above, Steffey et al. (1985) demonstrated respiratory effects caused by the administration of acepromazine alone in horses anaesthetised with halothane. In this study, general anaesthesia in horses was induced and maintained with halothane in oxygen for one hour before acepromazine was administered IV at either 0.033 mg kg\(^{-1}\) or 0.067 mg kg\(^{-1}\) and respiratory measurements continued for a further 120 minutes. Administration of acepromazine at both doses caused an increase in PaCO\(_2\) and a decrease in arterial pH attributed to respiratory acidosis. Interestingly, the respiratory rate, tidal volume and minute volume were unchanged following administration of acepromazine in these horses and the authors speculated the increase in PaCO\(_2\) was due to an increase in physiological dead space volume (Steffey et al., 1985).

The effect of premedication with acepromazine and butorphanol followed by induction of general anaesthesia with propofol in dogs was demonstrated by Kojima et al., (2002). Dogs that received 0.05 mg kg\(^{-1}\) acepromazine and 0.2 mg kg\(^{-1}\) butorphanol IM then propofol (mean induction dose of 3.8 ± 0.6 mg kg\(^{-1}\)) showed a decrease from baseline in PaO\(_2\) and an increase in PaCO\(_2\) immediately after tracheal intubation. The study also showed SaO\(_2\) decreased in dogs premedicated with acepromazine and butorphanol and induced with propofol. The changes observed were reported to be mild and did not reach significance however, the authors did report some cases of post-induction apnoea.

Studies investigating the respiratory effects of premedication of dogs with acepromazine undergoing general anaesthesia with injectable anaesthetic agents are lacking. Most of the studies published examine the effects of acepromazine in conscious animals. This gap in knowledge of what happens to some respiratory variables in healthy dogs following premedication with acepromazine and methadone in the immediate post-induction phase is part of the objective of this thesis.
2.2 The Respiratory Effects of Dexmedetomidine

Dexmedetomidine is an $\alpha_2$ adrenoreceptor agonist, frequently used in small animal anaesthesia to produce sedation, muscle relaxation and analgesia. Dexmedetomidine is the dextrorotatory isomer of the racemic drug medetomidine (Rankin, 2015). Studies evaluating the anaesthetic effects of medetomidine and its two isomers have indicated the D-isomer (dexmedetomidine) is responsible for the sedative and analgesic effects of medetomidine (Vickery et al., 1988; Savola and Virtanen, 1991; MacDonald et al., 1993; Kuusela et al., 2000) thus, in this review, studies reporting the effects of dexmedetomidine and/or medetomidine have been considered.

Alpha-2 adrenoreceptors are present in many different areas including neural tissue, many organs and in vascular tissue (Rankin, 2015). Binding of an $\alpha_2$ adrenoreceptor agonist can cause inhibition of adenylate cyclase, resulting in a decrease in the accumulation of cAMP. Activation of the $\alpha_2$ adrenoreceptors also activates potassium channels and inhibits voltage sensitive calcium channels (Maze and Tranquilli, 1991). While medetomidine and dexmedetomidine are both highly selective for the $\alpha_2$-adrenoreceptor, they do have some action on $\alpha_1$-adrenoreceptors as well (the $\alpha_2$: $\alpha_1$ specificity has been reported as 1620:1 for medetomidine) (Savola et al., 1986; Virtanen et al., 1988). The potential for a variety of undesirable effects related to the activation of central or peripheral $\alpha_1$ or $\alpha_2$ adrenoreceptors, as well as the desired effects of sedation and analgesia, has led to many studies in both animals and humans.

One of the earliest reports on the pulmonary effects of medetomidine in dogs was published by Bergstrom in 1988. In this general descriptive study in healthy Beagle dogs,
xylazine was compared to 3 different doses of medetomidine (10, 30 and 60 µg kg⁻¹) given alone or in combination with atropine as an intramuscular injection prior to induction and maintenance of general anaesthesia with thiopental and halothane respectively. The author reported a decrease in respiratory frequency during the sedation period (compared to prior to injection of xylazine or medetomidine) before induction of general anaesthesia however, they did not report if the decrease was statistically significant. In addition, PaO₂ and PaCO₂ were not reported for this phase of the study to enable evaluation of the clinical significance of this change. It was noted in the discussion that there was an increased risk of apnoea after induction of anaesthesia with thiopental in dogs that had been sedated with all the drugs tested and the author made the recommendation that pre-medication prior to anaesthesia only be performed in veterinary hospitals where staff were trained in management of unexpected apnoea (Bergstrom, 1988). Vainio and Palmu (1989) reported similar findings in Beagle dogs given 40, 80 or 160 µg kg⁻¹ medetomidine given IM and IV, with a significant decrease in respiratory frequency observed in the first 30 minutes after drug administration, which persisted for approximately 2 hours before gradually returning to control rates. As in the study by Bergstrom, PaO₂ and PaCO₂ were not measured to assess the clinical significance of the change in respiratory rate. In addition, the authors noted that, while the respiratory frequency decreased significantly, it did remain within the normal limits for healthy dogs (Vainio and Palmu, 1989).

The respiratory effect of medetomidine administered with fentanyl for sedation was reported in 1989 by England and Clarke. Female dogs in one group were administered either 20 or 40 µg kg⁻¹ of medetomidine IM, followed approximately 20 minutes later by 2 µg kg⁻¹ of fentanyl IV, while male castrated dogs in a second group were given 40 µg kg⁻¹ of medetomidine IM, followed approximately 20 minutes later by 2 µg kg⁻¹ fentanyl IV. In both groups, a significant decrease in respiratory rate was observed after medetomidine
administration. Arterial blood oxygen tension decreased within 15 minutes of injection of medetomidine but this decrease did not reach statistical significance. Arterial carbon dioxide tension remained within normal limits following medetomidine but did increase significantly following administration of fentanyl. Low $P_{\text{V}}O_2$ was also detected, although arterial oxygen saturation remained greater than 95%, even in dogs exhibiting cyanosis. One explanation offered for this phenomenon was that slow venous filling allowed for greater oxygen extraction due to low cardiac output. There were a significant number of subjects where arterial blood samples could not be obtained, which may have contributed to the inability to detect a significant difference in some variables. However, the results of this study suggest there may be some depressive effects on ventilation caused by medetomidine, and the administration of fentanyl enhanced these effects.

Bloor and colleagues (1989) conducted more extensive experiments to investigate the respiratory effects of medetomidine in dogs. Chronically tracheostomised dogs were anaesthetised with isoflurane. After a period of stabilisation control measurements of ventilatory and haemodynamic variables were recorded and the hypercapnic ventilatory response was assessed (where hypercapnia should induce increased ventilation in an attempt to reduce $P_{\text{a}}CO_2$). Dogs were then administered 20 $\mu$g kg$^{-1}$ medetomidine IV over 30 minutes, isoflurane was discontinued at the completion of medetomidine administration and 15 minutes later all measurements were repeated. The study found the mean slope of the hypercapnic response graph (plotting minute ventilation against $P_{\text{E}}CO_2$) was significantly increased following medetomidine compared to isoflurane, but when compared to a previous study in awake dogs the hypercapnic response following medetomidine was blunted (Hirshman et al., 1977; Bloor et al., 1989). The influence of using isoflurane prior to and during administration of medetomidine was not addressed in this study, and the authors reported there was still 0.3% end-tidal isoflurane detected when measurements began for the
medetomidine phase. Given that levels of 0.125% of isoflurane (0.1 minimum alveolar concentration (MAC) in humans) can cause depression of peripheral chemoreceptors to elevated CO₂ in humans (van den Elsen et al., 1998), it is possible the presence of isoflurane in the circulation (as indicated by detectable end-tidal isoflurane concentrations) influenced the results reported by Bloor et al. (1989) and may have over-estimated the ventilatory depressive effects of medetomidine in dogs. The addition of a control group that did not receive medetomidine would have aided in defining the respiratory effects of medetomidine more clearly.

In rats, dexmedetomidine was demonstrated to have little or no respiratory effects as determined by no change in arterial pH or PaCO₂ (Furst and Weinger, 1990). In this study, rats were premedicated with one of two doses of dexmedetomidine, saline or a combination of dexmedetomidine and idazoxan (an α₂ antagonist) and then given alfentanil 15 minutes later. All groups developed respiratory acidosis following administration of alfentanil, although the degree of acidosis was less in rats pre-treated with the higher dose of dexmedetomidine. In contrast, respiratory depression, although classed as minor, was detected in rats in a study reported by Bol et al. (1997). Rats were administered various doses of dexmedetomidine as 10 minute infusions with periodic arterial blood sampling starting at the onset of drug infusion. All rats showed a statistically significant decrease in pH, increase in PaCO₂, and decrease in PaO₂ and SaO₂ at the end of the infusions. The duration of these changes was not reported however, and the authors described the ventilatory depressant effects as minor. Respiratory depression was also detected in New Zealand white rabbits administered various doses of dexmedetomidine IV by Zornow (1991). In this study, respiratory rate and PaCO₂ increased in a dose-dependent manner and remained elevated until 60 minutes following drug administration (the end of the study), the increases in PaCO₂ being significant at all doses. PaO₂ decreased in all groups and this decrease persisted for 25
minutes following drug administration. Species differences in drug effects, differences in methodology and drug doses used may account for the different results obtained in these studies.

The respiratory effects of dexmedetomidine at various doses in dogs was investigated by Nguyen et al., in 1992. Increasing doses from 1 µg kg\(^{-1}\) to 100 µg kg\(^{-1}\) of dexmedetomidine were administered to healthy dogs with permanent tracheostomies. Inspired and expired gases were measured and controlled by connecting an open breathing circuit to the tracheostomy tube and this was also used to perform hypercapnic and hypoxic response tests. Responses to increasing inspired concentration of CO\(_2\) and decreasing inspired concentration of O\(_2\) were measured in awake dogs, dogs sedated with an IV bolus of either 1, 10, 20 or 100 µg kg\(^{-1}\) dexmedetomidine, and in dogs anaesthetised with isoflurane with and without a single IV bolus of 3 µg kg\(^{-1}\) dexmedetomidine. The results indicated that dexmedetomidine alone at a dose of 1 µg kg\(^{-1}\) caused a slight decrease in minute ventilation, but at doses greater than 10 µg kg\(^{-1}\) up to 100 µg kg\(^{-1}\) there was a progressive increase in minute ventilation. No dose between 1 µg kg\(^{-1}\) and 10 µg kg\(^{-1}\) was investigated.

Despite the increase in minute ventilation at higher doses, Nguyen et al., (1992) reported that there was a significant decrease in the slope of the hypercapnic response curve reported at all doses of dexmedetomidine trialled, although there was no change in the hypoxic response curve at any dose. The study also found that a dose of 3 µg kg\(^{-1}\) when combined with 0.37% isoflurane (the % isoflurane determined to be 1 minimum alveolar concentration (MAC) in dogs following 3 µg kg\(^{-1}\) dexmedetomidine IV) caused end tidal carbon dioxide (Pr\(_{\text{CO}_2}\)) to decrease and end tidal oxygen (Pr\(_{\text{O}_2}\)) to increase, caused no change in minute ventilation and no change in either the hypoxic or hypercapnic response curve when compared to awake dogs or dogs anaesthetised with 1.3% isoflurane (1 MAC.
isoflurane alone). However, in dogs anaesthetised with 1.5% isoflurane, a dose of 3 µg kg⁻¹ dexmedetomidine IV caused P_E CO₂, and PaCO₂ to increase compared to 1 MAC isoflurane alone and P_E O₂, PaO₂, arterial pH and the hypercapnic response slope to all decrease. These changes in ventilation markers were similarly altered by a dose of 20 µg kg⁻¹ dexmedetomidine IV, although in 4 out of 6 dogs given this treatment there was no detectable hypercapnic response at all (Nguyen et al., 1992). The results of this study suggest there is a synergistic effect of dexmedetomidine in isoflurane anaesthetised dogs resulting in dose-dependent respiratory depression. However, the effects of dexmedetomidine in awake dogs is less clear, as there appears to be a point at which increasing the dose of dexmedetomidine causes a change from ventilatory depression to stimulation of ventilation, but the dose at which that occurs was not determined in this study.

Another study which appears to indicate high doses of medetomidine has a stimulatory effect on respiration was published by Hayashi et al. in 1995. Dogs were administered 80 µg kg⁻¹ medetomidine, or a combination of 20 µg kg⁻¹ medetomidine with 0.3 mg kg⁻¹ midazolam IM and arterial blood samples were serially analysed for 120 minutes. Dogs receiving medetomidine alone had significantly higher PaO₂ over time than prior to drug administration, with concomitant reductions in PaCO₂. However, these dogs also had a significant reduction in oxygen delivery, with increased oxygen consumption and oxygen utilisation ratio. Dogs in the combination drug group showed no change in PaO₂ or PaCO₂ over time, while oxygen delivery decreased and oxygen utilisation ratio increased. The authors did not comment extensively on the respiratory effects of medetomidine, except to say the combination of medetomidine with midazolam had minimal effects on the respiratory system. The changes in oxygen delivery and consumption were attributed to a change in oxygen demand and the authors believed oxygen supply was sufficiently maintained in dogs receiving the medetomidine-midazolam combination. Unfortunately, no other respiratory
data (such as respiratory rate, minute ventilation volumes, $P_eCO_2$ etc.) were reported in this study which would have added to the overall understanding of these results.

In 1993, Cullen and Reynoldson compared the cardiopulmonary effects of medetomidine to that of xylazine as a premedication prior to propofol anaesthesia in dogs. In this study comparisons between propofol alone (6.55 mg kg$^{-1}$), medetomidine or xylazine alone and either medetomidine or xylazine followed by propofol (3 mg kg$^{-1}$) were made using cardiopulmonary variables as well as duration of sedation or anaesthesia. Of interest are the comparisons between medetomidine and medetomidine with propofol. Dogs given 30 $\mu$g kg$^{-1}$ medetomidine IM only showed a decrease in respiratory frequency 5 minutes after drug administration, although the authors noted one dog in this group panted for the duration of the experiment after drug administration. Propofol was administered over 15 seconds, and all dogs receiving propofol (either alone or following medetomidine) had a period of apnoea immediately following drug administration. The duration of apnoea was increased from 24 ± 4 seconds in the propofol alone group to 39 ± 7.3 seconds in the group receiving medetomidine and propofol however this difference was not statistically significant. A trend toward decreasing respiratory frequency with corresponding decreased $PaO_2$ and increased $PaCO_2$ was noted from 3 minutes onwards after propofol administration. Interestingly, the authors of this study attributed all the observed respiratory depressant actions noted in dogs receiving propofol (decreased $PaO_2$, increased $PaCO_2$, and apnoea) to propofol alone, despite the apparent trend toward increased respiratory depression in dogs receiving both propofol and medetomidine, which could suggest a synergistic effect on respiration from the two drugs when administered together. While there were no statistically significant changes in $PaO_2$ in dogs receiving only medetomidine in this study, there was a trend toward decreasing $PaO_2$ and there was a significant increase in $PaCO_2$ 10 minutes after medetomidine was given.
In contrast to results obtained by Cullen and Reynoldson (1993), Pettifer and Dyson (1993) observed a significant decrease in respiratory rate in dogs receiving medetomidine IM or IV which persisted for 180 minutes after drug administration (the end point of data collection). No significant changes in PaO$_2$ or PaCO$_2$ were observed at the 4 time points throughout the study when arterial blood samples were acquired. The lack of change in arterial blood gas tensions despite decreased respiratory rate was attributed to an increase in tidal volume, although this was not measured during the experiment (Pettifer and Dyson, 1993). Venugopalan et al., (1994) also observed a significant decrease in respiratory rate over time in dogs receiving medetomidine either IV (30 µg kg$^{-1}$) or IM (40 µg kg$^{-1}$). Similarly, Ko et al. (1994) reported a decrease in respiratory frequency at 5 and 10 minutes after administration of 15 µg kg$^{-1}$ medetomidine combined with 0.044 mg kg$^{-1}$ atropine IM, and the decrease in respiration rate continued following administration of 0.5 mg kg$^{-1}$ etomidate IV. Arterial partial pressure of oxygen and PaCO$_2$ were measured periodically for 180 minutes following drug administration in the study by Venugopalan et al. (1994) and for 75 minutes in the study by Ko et al. (1994). Unlike the results reported by Cullen and Reynoldson (1993), Venugopalan et al. (1994) found no significant change in PaCO$_2$ in any group over time, however there was a significant decrease in PaO$_2$ in both IV and IM groups in the first 30 minutes after medetomidine administration, followed by a progressive increase in PaO$_2$ for the remainder of the experiment. The authors attributed the progressive increase in PaO$_2$ to increasing tidal volume as compensation for the decreased respiratory rate. The study by Ko et al. (1994), on the other hand, found that with continued anaesthesia using etomidate as a continuous rate infusion (CRI) the PaCO$_2$ did increase following induction of general anaesthesia with etomidate, although there was no change in PaO$_2$ over time. The difference in results between these studies supports the supposition that when given alone, medetomidine likely has only a small effect on respiratory function (if measured simply by
respiratory rate or PaCO₂) however, when given in conjunction with an induction agent such as propofol or etomidate the respiratory effects are likely more profound.

The effects of spinal and systemically administered dexmedetomidine were evaluated in dogs by Sabbe et al. (1994). Chronically tracheotomised Beagle dogs were trained to tolerate tracheal intubation through the tracheostomy and to rebreathe in to a closed system to assess the respiratory effects of dexmedetomidine when administered systemically or spinally. Intravenous and epidural administration of 10 µg kg⁻¹ and 50 µg of dexmedetomidine respectively resulted in a significant decrease in the slope of the CO₂ response curve that persisted for up to 2 hours. Intracisternal administration of 1 µg kg⁻¹ dexmedetomidine had no effect on the CO₂ response curve. A significant decrease in respiratory rate after intravenous dexmedetomidine was observed however, there were no significant changes in PĖCO₂. The results from the study by Sabbe et al. (1994) correlate with those of Bloor et al. (1989) and Nguyen et al., (1992) and also suggests that the respiratory effects of dexmedetomidine are primarily due to supraspinal effects, as there were no respiratory changes observed until very high doses were given epidurally. Sabbe et al. (1994) also argued that, as there were no respiratory effects observed with intracisternal administration of dexmedetomidine, the site of receptors causing respiratory depression would have to be distal to the site of delivery in the cisterna and that the respiratory depression caused by high doses of dexmedetomidine given epidurally was likely due to systemic distribution of the drug, and not spinal redistribution. The clinical significance of reduced respiratory rate and decrease in the CO₂ response curve reported in this study was not addressed but could be assessed by analysis of arterial blood gas tensions and pH.

Several studies have included the use of arterial blood gas tensions as part of analysis of the utility of medetomidine in dogs. Alibhai et al., (1996) evaluated the use of 40 µg kg⁻¹ medetomidine alone or given before or after 30 µg kg⁻¹ atropine in healthy Beagle dogs and
reported no significant changes in arterial pH, PaCO$_2$ or PaO$_2$ over 60 minutes after administration of medetomidine. Respiratory rates were not reported however, the authors reported a periodic respiratory pattern occurred in all group, where dogs would take several short, shallow breaths then would become apnoeic for up to 45 seconds. Kramer et al., (1996) compared the efficacy of two doses of either IV or IM medetomidine (40 µg kg$^{-1}$ or 80 µg kg$^{-1}$) with xylazine and L-methadone for various procedures in a clinical trial. Dogs that became very deeply sedated in the medetomidine groups developed a periodic breathing pattern with periods of apnoea, similar to that reported by Alibhai et al., (1996). This study also found medetomidine caused a decrease in the respiratory frequency within 15 minutes of drug administration, although there were no significant changes in acid/base blood values. In 2000, Kuusela et al. reported a decrease in respiratory rate, pH and PaO$_2$ in healthy dogs administered 40 µg kg$^{-1}$ medetomidine IV or 10 or 20 µg kg$^{-1}$ dexmedetomidine IV however, these changes were still within clinically normal limits and PaCO$_2$ did not change. This same research group also examined the effects of a continuous infusion of levomedetomidine before an IV bolus of 10 µg kg$^{-1}$ dexmedetomidine in laboratory-trained dogs (Kuusela et al., 2001a). There was no change in respiratory variables during the levomedetomidine infusion, when dexmedetomidine was administered there was a decrease in respiratory rate, pH and PaO$_2$ and PaCO$_2$ increased and again, like the previous study, these changes still remained within clinically normal limits. These studies indicate that, when given alone, medetomidine does have some effect on respiration although the effects do not alter variables beyond clinical normal limits in healthy animals. The effect of these respiratory changes in dogs with compromised respiratory function have not been studied but it is possible they may be more detrimental.

Medetomidine was compared to dexmedetomidine as a premedication treatment in dogs undergoing propofol and isoflurane anaesthesia by Kuusela et al. (2001b). Dogs
received one of three different doses of medetomidine or dexmedetomidine IV, followed by
induction of anaesthesia with propofol (administered until it was possible to intubate the
trachea), which was then maintained with isoflurane in oxygen. In the time after
premedication but before induction of anaesthesia with propofol no differences in PaO₂ or
PaCO₂ were observed in any medetomidine or dexmedetomidine groups. After induction
with propofol (the mean induction dose depended on the medetomidine or dexmedetomidine
dose administered) however, a significant increase in PaCO₂ was observed in all groups and
dogs receiving the highest dose of medetomidine and dexmedetomidine had a slight but
statistically significant decrease in PaO₂. There was also no change in respiratory rate after
premedication with medetomidine or dexmedetomidine at any dose trialled. However, at 10
minutes after induction there was a slight but significant decrease in respiratory rate in dogs
receiving the highest and middle doses of medetomidine and dexmedetomidine. There were
no significant changes in arterial haemoglobin oxygen saturation (SpO₂) in any group at any
time. The respiratory effects of medetomidine or dexmedetomidine reported in this study by
Kuusela et al. (2001b) are more in line with the results reported by Bloor et al. (1989);
Nguyen et al. (1992); Cullen and Reynoldson (1993) and Ko et al. (1994) and indicate there
is likely a synergistic effect of the α2 adrenoceptor agonist with drugs commonly used to
both induce and maintain anaesthesia in dogs.

The studies discussed above evaluated the respiratory effects of medetomidine
primarily through analysis of arterial blood gas changes, respiratory frequency or alveolar gas
concentration changes. These methods can detect hypoventilation, however do not
characterise the neurorespiratory drive to breathe that is controlled by the central nervous
system respiratory centres. The effect of medetomidine on central respiratory neuromuscular
drive in conscious dogs was investigated by Lerche and Muir (2004) by determining
inspiratory occlusion pressure while delivering increasing concentrations of inspired CO₂.
Lerche and Muir (2004) found that doses of 5 or 10 µg kg\(^{-1}\) medetomidine IV caused a decrease in respiratory centre sensitivity and neurorespiratory drive in response to increasing inspired CO\(_2\), as evidenced by decreased respiratory rate, tidal volume, minute ventilation and inspiratory occlusion pressure compared to dogs not receiving medetomidine. The authors postulated that the decreased ventilatory drive observed could be due to inhibition of excitatory stimuli to the respiratory centres, due to the central activation of \(\alpha_2\) adrenoreceptors in the locus coeruleus extending to other parts of the brainstem. An inhibitory effect of medetomidine on peripheral chemoreceptors as well as directly on central respiratory centres was also suggested as a mechanism of action for respiratory depression in this study. The doses of medetomidine used in this study more closely correlate with those typically used in preanaesthetic combinations of drugs in dogs, thus these results are highly relevant. The respiratory depression observed by these doses of medetomidine alone was significant, and the clinical significance of the central respiratory effects of medetomidine are potentially greater than initially thought.

The studies reviewed here suggest that the respiratory effects of dexmedetomidine are dose-dependent. At clinically used doses in premedication of healthy dogs prior to anaesthesia there does appear to be some respiratory depressant effects of dexmedetomidine. The possibility of a synergistic effect of dexmedetomidine with other anaesthetic agents on respiratory function has not been fully evaluated in dogs and is an area where further research is warranted.
2.3 The Respiratory Effects of Alfaxalone

Alfaxalone is a neuroactive steroid molecule first described for use as an intravenous anaesthetic induction agent in animals in 1971 by Child et al. The original formulation used from the early 1970’s until the late 1990’s combined alfaxalone with alphadolone, another steroidal anaesthetic, dissolved in polyethoxylated castor oil (Cremophor ® EL) and was marketed as Althesin (human use) or Saffan (animal use). The Cremophor ® EL component of the mixture caused histamine release and frequent anaphylactoid reactions in many species (Keates, 2003; Ferré et al., 2006) and in the early 2000’s a water-soluble formulation of alfaxalone alone dissolved in the 2-hydroxypropyl-beta-cyclodextrin carrier was released for use in dogs and cats in Australia (Alfaxan ®). This formulation had no reported histamine release following injection and has now replaced Saffan in veterinary anaesthesia. As some early investigations using Saffan or Althesin have not been repeated with the new formulation Alfaxan®, papers reporting the effects of any of the three preparations have been reviewed in this chapter, with a focus on the respiratory effects of these drugs.

Alfaxalone modulates the activity of the GABA$_A$ receptor in the central nervous system in a dose-dependent manner, the overall effect is enhancement of the action of the inhibitory neurotransmitter GABA (Lan and Gee, 1994; Lambert et al., 2003). Voltage-clamp studies using bovine chromaffin cells indicate concentrations of 30 nM – 300 nM alfaxalone prolongs the GABA$_A$ channel open time, while concentrations > 1 µM alfaxalone directly activates the chloride channel linked to the GABA$_A$ receptor (Cottrell et al., 1987). It appears that alfaxalone has similar effects to benzodiazepines, barbiturates, etomidate, and propofol on the modulation of GABA responses, however it binds to different sites on the GABA$_A$ receptor to those of the benzodiazepines and phenobarbitone (Harrison and Simmonds, 1984; Cottrell et al., 1987; Akk et al., 2007).
The anaesthetic effects of the combination of alfaxalone and alphadolone in a variety of species were reported in 1971 by Child et al. The study reported the results of many different experiments, including the determination of the anaesthetic dose 50, lethal dose 50, anaesthetic duration of various doses of alfaxalone/alphadolone, cardiovascular effects, and the effect of some premedication agents on the duration of anaesthesia, with the majority of experiments being conducted in domestic cats. The respiratory effects of alfaxalone/alphadolone were not investigated in great detail, however the authors did report that in the first 5 minutes after injection of 1.2 mg kg⁻¹ in cats there was “little effect” on respiration. The effect of a dose of 19.2 mg kg⁻¹ on 3 cats had a mixed effect on respiration, one cat had a reduced respiratory rate and 2 cats had an increase in respiratory rate (Child et al., 1971). The study did not investigate more specific respiratory effects of alfaxalone/alphadolone except to say that in prolonged infusions of the drug some animals experienced respiratory depression at high doses. While the article stated the experiments performed were designed to simulate clinical conditions where alfaxalone/alphadolone would be used, it was published at a time before the common practice of administering sedation agents before inducing general anaesthesia in animal patients, and the premedication agents that were tested in the study are no longer commonly used (except perhaps for the combination of atropine and pethidine). The small number of study animals and lack of specific data on respiratory function severely limit the ability to interpret the respiratory effects of alfaxalone/alphadolone observed in this report and correlate them with those seen in a modern veterinary clinical setting.

Althesin (alfaxalone/alphadolone) caused post-induction apnoea in human subjects given either 50 µl kg⁻¹ or 100 µl kg⁻¹ following premedication with diazepam and atropine or papaveretum (a mixture of predominately morphine and codeine opiates) and hyoscine (Hall et al., 1973). The overall incidence of post-induction apnoea was 41% of patients with a
mean duration of 35.6 ± 25.5 seconds. People receiving 100 µl kg\(^{-1}\) Althesin had a higher incidence of post-induction apnoea (50% overall) compared to those receiving the lower dose (32.5% overall). This study also found a significant reduction in minute volume in all groups at 2 and 3 minutes after induction of anaesthesia. While it is not possible to know the exact amount of Althesin administered in this study (as the drug concentration was not reported), the results suggest the administration of higher doses of Althesin causes more apnoea in human subjects than lower doses. Savege \textit{et al.}, (1973) found a dose of 50 µl kg\(^{-1}\) Althesin in healthy, unpremedicated humans caused a characteristic respiratory pattern of deep breaths followed by a brief period of apnoea lasting up to 36 seconds, then rapid shallow breathing. There was a mild increase in PaCO\(_2\) from pre-induction values at 6 minutes after induction in this study population, and a small decrease in PaO\(_2\), however neither of these changes reached significance. The respiratory effects of alfaxalone/alphadolone in pigs premedicated with atropine was found to be similar to those described in humans when administered IV at doses of 2, 2.5 and 3 mg kg\(^{-1}\) (Cox \textit{et al.}, 1975). This preliminary study reported there was “minimal respiratory depression”, post-induction apnoea was “usually absent” and did not exceed 15 seconds when it did occur, and some pigs developed rapid shallow breathing patterns after induction of anaesthesia. These initial studies using a drug that was new at the time suggested that Althesin does cause mild respiratory depression in humans, and this depression appears to be influenced by the dose administered, although again a lack of detail in these reports limits contemporary interpretation.

A more comprehensive investigation into the respiratory effects of Althesin in human and feline subjects was published in 1978 by Gautier and Gaudy. In this study, the effect of three different intravenous induction agents (one being Althesin) on the tidal volume-inspiratory duration relationship was evaluated in humans and domestic cats. The authors reported a significant difference of effect of anaesthetic agent in humans compared to cats, in
that anaesthetic agents appear to cause an increase in breathing rate with decreased tidal volume in humans, but an opposite effect was observed in cats. The contradictory results observed in this study highlight the potential danger in extrapolating information from one species to another.

In 1980 a report was published that compared induction of general anaesthesia with Althesin and a new drug, Diprivan (propofol), in humans (Kay and Stephenson, 1980). The respiratory effects observed with administration of Althesin in this study concurred with the results of earlier studies, in that no significant change in respiratory rate was observed. The administration of propofol did cause a significant decrease in respiratory rate, and also a decrease in the “respiratory depth”, which was significantly lower than baseline measurements, and significantly different from the Althesin group. In contrast, Quail et al., (1985) reported an initial decrease in respiratory frequency in human subjects administered Althesin following administration of epidural bupivacaine, before respiratory rates returned to pre-Althesin levels. The time taken for respiratory frequency to return to baseline levels was not reported. In the same article, Quail and colleagues also investigated the effects of Althesin in rabbits at increasing dose rates and found there was a dose-related decrease in minute ventilation and respiratory frequency in this species.

Dose-related decreases in ventilation, PaO₂ and an increase in PaCO₂ were also observed in dogs anaesthetised with Althesin in a study conducted by Gaudy et al. in 1984 evaluating the effect of oxygen on hypoxic ventilatory drive. Dogs were administered Althesin as a constant infusion from the start of induction of general anaesthesia until a steady state was reached at a light plane of anaesthesia, ventilation measurements were made and arterial blood sampled for analysis. Depth of anaesthesia was increased by increasing the rate of administration of Althesin, and after a period of stabilisation at the new rate the ventilation and blood gas measurements were repeated. There was a significant decrease in
respiratory rate and minute ventilation, increase in PaCO$_2$ and decrease in PaO$_2$ and pH when the depth of anaesthesia was increased by increasing the dose of Althesin delivered. Gaudy and colleagues (1986) repeated these experiments without a period of hypoxia and found after induction of anaesthesia with Althesin the minute ventilation, tidal volume and PaO$_2$ were decreased compared to normal values in conscious dogs previously reported by Stahl (1967). When the results of these two studies are evaluated together, there is evidence that Althesin causes respiratory depression when used to induce general anaesthesia in dogs, and the effect of increasing the dose of Althesin administered suggests a dose-dependent effect on respiration, which could have implications for the effect of rate of administration of Althesin at induction.

The prevalence of anaphylactoid reactions in response to Saffan or Althesin anaesthesia prevented extensive research of this drug in dogs during the late 1980’s-1990’s. One study in 1987 examined the cardiopulmonary effects of Saffan in cats at a dose of 12 mg kg$^{-1}$ IV (Dyson et al., 1987). This dose caused significant respiratory depression at 5, 10 and 15 minutes after induction of anaesthesia, the authors reported one incidence of apnoea (out of 8 anaesthetic events) that lasted 5 minutes. There were no statistically significant changes in arterial blood gas tensions after administration of Saffan, although a trend toward increasing PaCO$_2$ and decreasing PaO$_2$ was detected but both variables stayed within clinically acceptable limits throughout the experiment. The authors speculated there was a compensatory increase in tidal volume in response to the decreased respiratory rate. The results of this study were the opposite of the findings reported by Middleton et al., (1982) where hyperventilation was observed in cats receiving 9 mg kg$^{-1}$ Saffan IV. In that study, hypotension was also observed and this was thought to be one stimulus inducing hyperventilation. However, hypotension was also observed in the study by Dyson et al.,
(1987) and yet hyperventilation did not occur, raising doubt over some of the conclusions of Middleton et al., (1982).

The anaphylactoid effects of Cremophor ® EL in dogs and cats lead to the reformulation of alfaxalone in 2-hydroxypropyl-beta-cyclodextrin and this formula became available in Australia in 2000. Research continued with this new formulation and in 2003 the results of some pre-registration safety studies were presented at the American Academy of Veterinary Pharmacology and Therapeutics Symposium (Pearson et al., 2003). Alfaxalone caused apnoea immediately after induction in both cats and dogs and the duration of apnoea increased with increasing dose rates of alfaxalone. Respiratory depression was also reported to be dose dependent, moderate depression occurring at lower doses, and severe respiratory depression in most animals at high doses. It was noted that there was marked individual variation in susceptibility to the effects of alfaxalone on respiratory function (Pearson et al., 2003). In 2008, Ambros et al., compared the use of this new alfaxalone with propofol as both an anaesthetic induction and maintenance agent in 6 crossbreed dogs. Dogs were administered 0.02 mg kg⁻¹ acepromazine and 0.05 mg kg⁻¹ hydromorphone (a pure µ opioid) IV 30 minutes prior to induction with either alfaxalone (2 mg kg⁻¹) or propofol. One dog had a period of apnoea (defined in this study as a period of no spontaneous breathing for 30 seconds or longer) immediately after induction with alfaxalone. Overall there was no statistically significant change in respiratory rate after induction with alfaxalone, although there was a decreasing trend in rate over time. The pH was decreased 5 minutes after induction and this decrease persisted for the duration of the experiment. There was also a brief increase in PaCO₂ 5 minutes after induction, which subsequently resolved as anaesthesia progressed. The authors in their discussion speculated that the addition hydromorphone as part of the premedication combination contributed to the observed respiratory depression noted after induction of anaesthesia due to the known effect of opioids causing decreased
response in the respiratory centre to hypercapnia. This study highlights the potential for synergism between drugs used for premedication and induction of anaesthesia which can influence adverse effects observed in the subsequent anaesthetic period. The small sample size likely precluded the detection of significant differences between alfaxalone and propofol, and possibly individual patient variation as well.

The effects of clinical and supraclinical doses of alfaxalone in dogs were also reported in 2008 by Muir et al. Doses of 2, 6 and 20 mg kg\(^{-1}\) alfaxalone were administered IV over 60 seconds and changes in respiratory rate, pH, arterial blood gas tensions, tidal volume, minute volume, and duration of apnoea were recorded. Alfaxalone caused a dose-dependent decrease in respiratory rate, minute volume, and PaO\(_2\). The reduction in PaO\(_2\) at all doses at 1 minute after induction was enough to be classified as hypoxaemia in healthy dogs, although the difference in the 2 mg kg\(^{-1}\) group was not statistically significant. There was no significant change in tidal volume, and there was no change in PaCO\(_2\) in dogs administered 2 mg kg\(^{-1}\) alfaxalone however, at higher doses PaCO\(_2\) increased. The mean duration of apnoea ranged from 30 seconds in the 2 mg kg\(^{-1}\) dose group, to 60 seconds in the 20 mg kg\(^{-1}\) dose group. The authors of this study did not directly compare alfaxalone to other IV anaesthetic agents in the experimental design but despite this speculated that based on previous studies the results of their trial indicated alfaxalone produced less respiratory depression than propofol or thiopentone. This study was a small laboratory trial in 8 purpose-bred dogs which did not utilise any sedative premedication agents and may therefore be of limited clinical relevance.

In contrast to the study by Muir et al. (2008), Maddern et al. (2010) reported only once case of apnoea out of 85 dogs that were administered alfaxalone IV after premedication with either medetomidine (4 µg kg\(^{-1}\) IM), butorphanol (0.1 mg kg\(^{-1}\) IM), or a combination of medetomidine and butorphanol. This clinical study administered alfaxalone at a slow rate (0.5 mg kg\(^{-1}\) over 60 seconds initially, then 0.2 mg kg\(^{-1}\) every 20 seconds) until tracheal
intubation was possible. As well as the very low incidence of post-induction apnoea, the study also reported a much lower mean induction dose of alfaxaline (0.8 ± 0.3 mg kg\(^{-1}\) in dogs receiving medetomidine and butorphanol) required to allow intubation that had previously been reported. The authors attributed these findings to the method of administration of alfaxalone (i.e. slowly to a given effect, that of being able to intubate the trachea) and proposed that the longer time of administration of drug allowed larger concentrations of alfaxalone to reach the effect site in the brain at lower administered doses, which would result in less negative effects such as apnoea.

Other studies analysing the effects of alfaxalone for induction of anaesthesia in dogs without the use of any premedication sedative or analgesic agents were reported by Keates and Whittem, (2012); Morgaz Rodriguez et al., (2012); and Maney et al., (2013). Morgaz Rodríguez et al. (2012) compared the cardiorespiratory effects and quality of induction of alfaxalone with etomidate in eight healthy adult Beagle dogs. Alfaxalone was administered to effect until it was possible to intubate the trachea and animals breathed room air during the experiments. There was a significant decrease in respiratory frequency observed immediately after induction of anaesthesia, however there was no incidences of post-induction apnoea and PaCO\(_2\) did not change significantly after induction. There was however, a significant reduction in PaO\(_2\) and SaO\(_2\) and all animals were hypoxaemic immediately after induction. Keates and Whittem (2012) compared the respiratory effects of alfaxalone after induction of anaesthesia with those of propofol. Increasing doses of 1, 2, 5, 10, and 20 times the labelled doses of alfaxalone (2 mg kg\(^{-1}\)) and propofol (6.5 mg kg\(^{-1}\)) were administered to healthy crossbreed dogs until the dogs became apnoeic (defined in this study as lack of spontaneous breathing for 60 seconds or longer) at which point they were removed from the study and did not move on to the next dose group. The authors reported that more dogs became apnoeic at lower multiples of the labelled dose of propofol than alfaxalone. One dog that received 10x
the labelled alfaxalone dose did not develop apnoea but did exhibit a severe drop in SpO2 to 30%. The authors concluded that propofol had a narrower safety margin than alfaxalone with regards to respiratory function. The rate of administration of the drugs changed with each dose as the total volume was consistently given over 60 seconds, meaning that more drug was given more quickly at the higher multiples of the dose. This may have affected the incidence of apnoea observed in both groups. The study design also limited the ability to collect complete data sets, as some dogs had recovered from the single bolus of drug before initial data was collected, and the effect of propofol or alfaxalone on SpO2 and PeCO2 were not reported. In addition, invasive monitoring such as arterial blood gas tensions were not measured. While apnoea is a clinically important adverse event following induction of anaesthesia, it is not the only measure of respiratory depression and the lack of other data that could elucidate a more accurate picture of the degree of respiratory depression caused by either drug is a significant detractor from the conclusions of this study. The study by Maney et al. (2013) also compared the cardiorespiratory effects of induction of anaesthesia with alfaxalone or propofol in eight crossbreed dogs. Alfaxalone was administered IV to effect (able to intubate the trachea) and the respiratory frequency, SaO2, PaO2, PaCO2 and alveolar-arterial oxygen (P\textsubscript{A}O\textsubscript{2}-PaO\textsubscript{2}) gradient (among other variables) were monitored. Alfaxalone in this study caused a significant decrease in respiratory frequency immediately after induction and arterial blood pH decreased while PaCO\textsubscript{2} increased significantly. In contrast to some of the previous studies, there was no clinically or statistically significant decrease in PaO\textsubscript{2} (despite these dogs also breathing room air following induction) and there was no incidence of post-induction apnoea detected. There was a significant decrease in PaO\textsubscript{2} and SaO\textsubscript{2} immediately post-induction in dogs receiving propofol. The effects of alfaxalone on PaCO\textsubscript{2} was attributed to a decrease in minute volume, and the effects of propofol were attributed to a
mismatch in ventilation and perfusion as there was a significant increase in $\text{P}_{\text{A}}\text{O}_2$-$\text{PaO}_2$ gradient between baseline and post-induction.

Alfaxalone has been used in sick dogs with an anaesthetic risk American Society of Anesthesiologists (ASA) classification III-V in a small clinical trial comparing the cardiorespiratory effects of alfaxalone with an induction combination of fentanyl, midazolam and propofol (Psatha et al., 2011). All dogs in this study were premedicated with 0.2 mg kg$^{-1}$ methadone IM alone before induction of anaesthesia using alfaxalone given to effect. There were no incidents of post-induction apnoea in the alfaxalone group, although there was a decrease in respiratory rate immediately after induction. The study did not report if there were any changes in $\text{SpO}_2$ or $\text{PaO}_2$ after induction of anaesthesia. Another small study in 14 healthy crossbreed dogs used premedication with 0.01 mg kg$^{-1}$ acepromazine and 0.4 mg kg$^{-1}$ morphine subcutaneously (SC) before induction with alfaxalone or propofol (Suarez et al., 2012). Alfaxalone was administered over 40 seconds until tracheal intubation was possible and a mean induction dose of 1.9 mg kg$^{-1}$ was required. As in the study by Psatha et al. (2011), this study did not observe any post-induction apnoea. Unlike the Psatha study, there was no change in respiratory frequency from immediately prior to induction of anaesthesia (after premedication had been administered) to 5 minutes after induction. The difference in premedication drugs, the rate of administration of alfaxalone, and the health status of the dogs used in the study by Suarez et al. (2012) and Psatha et al. (2011) may explain the difference in respiratory frequency observed in the two studies. Arterial blood gas measurements were not taken until 35 minutes after induction and $\text{SpO}_2$ was not reported, so it is not possible to determine the immediate post-induction effects of alfaxalone on oxygen haemoglobin saturation in the study by Suarez et al. (2012). By comparison, Quirós Carmona et al. (2014) reported no cases of post-induction apnoea, but did find a significant decrease in $\text{PaO}_2$ and $\text{SaO}_2$ in both dogs given no premedication prior to induction with alfaxalone, and
dogs given 1 or 2 µg kg\(^{-1}\) dexmedetomidine IV prior to alfaxalone induction. The decrease in PaO\(_2\) was more pronounced in dogs receiving the higher dose of dexmedetomidine, and this group received a lower dose of alfaxalone (mean dose 2.08 ± 0.34 mg kg\(^{-1}\)) to enable tracheal intubation compared to the group receiving no premedication (mean alfaxalone induction dose 4.74 ± 1.61 mg kg\(^{-1}\)). This result suggests the combination of alfaxalone and dexmedetomidine may have a more significant effect on respiratory depression than either drug alone.

Alfaxalone at a dose up to 2 mg kg\(^{-1}\) has been administered IV over 60 seconds to 25 healthy puppies aged 12 weeks or less that were premedicated with 0.03 mg kg\(^{-1}\) acepromazine, 0.3 mg kg\(^{-1}\) morphine and 0.04 mg kg\(^{-1}\) atropine SC in a small clinical trial (O’Hagan et al., 2012). No change in respiratory frequency was detected and only one puppy had an episode of post-induction apnoea which lasted 50 seconds. The SpO\(_2\) immediately after induction of anaesthesia was clinically normal with a mean of 99%. A larger clinical trial of 60 healthy adult dogs that were premedicated with 0.03 mg kg\(^{-1}\) acepromazine and 3 mg kg\(^{-1}\) pethidine IM then induced with 1.5 mg kg\(^{-1}\) alfaxalone or 3 mg kg\(^{-1}\) propofol IV found a higher incidence of post-induction apnoea than that found in the study in puppies (Amengual et al., 2013). In the study by Amengual et al., 14 out of 29 dogs receiving alfaxalone had apnoea immediately after induction, 9 out of 29 dogs were apnoeic at 3 minutes after induction and 7 dogs were still apnoeic 5 minutes after induction. The authors stated too much missing data precluded statistical analysis of P\(_{E\text{-CO}_2}\), although the mean values for 0, 3 and 5 minutes after induction of anaesthesia were within clinically acceptable limits. As with the study by O’Hagan et al. (2012), SpO\(_2\) immediately after induction was normal and did not change in the first 5 minutes of anaesthesia. In contrast to the other studies previously discussed, the method of alfaxalone administration used in the Amengual study was very different, alfaxalone at 1.5 mg kg\(^{-1}\) was administered quickly over 5 seconds
in all cases. This rapid administration of alfaxalone may have resulted in a higher dose of alfaxalone than was required which may have increased the incidence of post-induction apnoea.

Herbert et al. (2013) reported the differences between 0.05 mg kg\(^{-1}\) acepromazine or 10 µg kg\(^{-1}\) dexmedetomidine combined with 20 µg kg\(^{-1}\) buprenorphine for IM premedication prior to induction of anaesthesia with alfaxalone administered over 60 seconds (mean induction dose 1.5 ± 0.57 mg kg\(^{-1}\)) in healthy dogs undergoing ovariohysterectomy surgery. Post-induction apnoea occurred in 10 of 38 dogs overall and the authors reported there was no difference in incidence of apnoea between dogs receiving acepromazine or dexmedetomidine. No other respiratory data from the induction time period were reported in this study. A clinical study in 50 dogs undergoing magnetic resonance imaging (MRI) by Okushima et al. (2015) also reported a higher incidence of post-induction apnoea than other studies, with 17 out of 25 dogs having apnoea. In both these studies a definition of apnoea was not provided (i.e. how long without a spontaneous breath constituted apnoea), thus it is difficult to directly compare these results to other studies as this information could significantly alter how many dogs would be classified as having apnoea or not. Lack of spontaneous breathing for > 30 seconds, the most commonly described definition of apnoea, was used by Pinelas et al. (2014) in a study designed to examine the effect of 1 or 3 µg kg\(^{-1}\) dexmedetomidine premedication combined with 0.2 mg kg\(^{-1}\) methadone IM on the induction quality and dose requirement of alfaxalone in 60 adult dogs undergoing elective procedures. Pinelas et al., (2014) found 7 out of 22 dogs that did not receive dexmedetomidine had a period of post-induction apnoea, compared to 11 out of 20 dogs receiving 1 µg kg\(^{-1}\) dexmedetomidine and 7 out of 18 dogs receiving 3µg kg\(^{-1}\) dexmedetomidine. The incidence reported in this study in all groups was similar to that observed in the study by Herbert et al. (2013) and Okushima et al. (2015), but was higher than that reported by Ambros et al.
(2008), Maddern et al. (2010) and Psatha et al. (2011). Interestingly, dogs receiving the lower
dose of dexmedetomidine had a higher incidence of apnoea than the high dose, although the
differences between all groups were not statistically significant. There was a significant
decrease in respiratory rate from immediately prior to induction of anaesthesia to 5 minutes
after tracheal intubation, and this decrease was seen in all groups. The authors did not report
specific data on the duration of apnoea in their study but did comment in the discussion that
the duration of apnoea appeared to follow a dose-dependent trend (of dexmedetomidine) and
speculated that the trend of increasing respiratory depression was due to the effects of the α2
adrenoreceptor agonist and opioid combination.

A study determining the pharmacokinetics and pharmacodynamics of the new
cyclodextrin formulation of alfaxalone in 6-8 cats after single and multiple repeated doses
(with no premedication) reported some clinical respiratory data and found a decrease in
respiratory rate at 5 minutes after induction of anaesthesia with 5 mg kg⁻¹ alfaxalone IV
(Whittem et al., 2008). This study reported no incidence of apnoea in any cats after either the
induction dose or repeated doses of 2 mg kg⁻¹ alfaxalone. Oxygen was not supplemented in
the anaesthetised cats however, and the mean SpO₂ at 10 and 15 minutes after induction of
anaesthesia was 88%, thus a state of hypoxaemia likely occurred in a majority of cats. This
result was not addressed in the discussion by the authors and potential reasons for the low
haemoglobin saturation values were not provided. It is possible this result occurred due to
factors unrelated to the administration of alfaxalone, however respiratory depression caused
by administration of alfaxalone leading to hypoxaemia cannot be excluded. If alfaxalone is
used in situations where oxygen is not supplemented and/or SpO₂ is not monitored it is
possible based on the results of this study that hypoxaemia could occur frequently which may
be harmful to patients, particularly those with decreased functional residual lung capacity or
those at increased risk of respiratory complications such as brachycephalic animals.
Another study that evaluated the clinical use of alfaxalone in cats was published by Martinez Taboada and Murison in 2010. This experiment used premedication of acepromazine 0.05 mg kg\(^{-1}\) IM and meloxicam (a non-steroidal anti-inflammatory agent) before administration of alfaxalone (or propofol) given until it was possible to intubate the trachea. Similar to the results of Whittem \textit{et al.}, (2008), no post-induction apnoea was detected in any cats in this study. The respiratory rate did decrease in the first 5 minutes after induction with alfaxalone and continued to decrease for the first 15 minutes of anaesthesia before gradually increasing again. The P\(_{E\ CO_2}\) initially increased slightly in the first 15 minutes after induction then gradually decreased, although the difference was not statistically significant. The authors postulated the lack of apnoea observed in their results could be due to the slow rate of administration until the desired effect was achieved (as opposed to giving a previously calculated dose entirely). In contrast to the results of Whittem \textit{et al.} (2008) no hypoxaemia was detected in this study, most likely due to the administration of supplemental oxygen via the endotracheal tube after intubation.

Further studies in cats attempted to evaluate the effect of different premedication agents on induction with alfaxalone, the suitability of alfaxalone as an agent for total intravenous anaesthesia, and the effect of the rate of administration on induction of anaesthesia with alfaxalone. Schwarz \textit{et al.}, (2014) compared the effect of administering 0.1 mg kg\(^{-1}\) acepromazine or 20 \(\mu\)g kg\(^{-1}\) medetomidine in combination with 0.2 mg kg\(^{-1}\) butorphanol IM on the induction characteristics and minimum infusion rates of alfaxalone for total intravenous anaesthesia. While an effect on induction dose requirements was detected (cats receiving acepromazine premedication required a mean of 2.57 ± 0.41 mg kg\(^{-1}\) compared to 1.87 ± 0.5 mg kg\(^{-1}\) alfaxalone in cats receiving medetomidine to achieve tracheal intubation), there was no post-induction apnoea detected in either group, although cats
receiving medetomidine had a higher respiratory frequency, and also higher \( \text{P}_{\text{e}}\text{CO}_2 \). \( \text{SpO}_2 \) was not significantly affected in either group, and overall the authors reported the respiratory variables remained within clinically acceptable limits. Beths et al., (2014) also reported no incidence of post-induction apnoea in cats administered alfaxalone for induction of anaesthesia following premedication with medetomidine and morphine. A decrease in respiratory frequency was detected after induction of anaesthesia in this study however, \( \text{SpO}_2 \) did not decrease significantly at any point. The authors hypothesised the lack of post-induction apnoea observed was due to the administration of alfaxalone slowly until tracheal intubation was possible.

The specific effect of the rate of administration of alfaxalone in cats was investigated in a pilot study by Bauquier et al., (2015). Cats in this study were premedicated with 20 \( \mu \)g kg\(^{-1}\) buprenorphine IM and 3 mg kg\(^{-1}\) alfaxalone SC prior to induction of anaesthesia with alfaxalone. Alfaxalone was administered via a syringe driver at either 2 mg kg\(^{-1}\) minute\(^{-1}\) or 0.5 mg kg\(^{-1}\) minute\(^{-1}\). There was a significantly higher dose of alfaxalone required for induction in the faster administration group. There was no difference in the incidence of post-induction apnoea, with 2 cats out of 6 in each group having a period of apnoea, although the duration of apnoea was not reported. These studies suggest rate of administration of alfaxalone does influence dose required to induce anaesthesia in cats however, the effect of rate of administration on respiratory changes are less clear, as both studies reported post-induction apnoea.

Various studies have attempted to determine the respiratory effects of alfaxalone in dogs with quite different results. When administered alone, alfaxalone appears to have minimal, or mild effects on overall respiratory function. However, even when administered alone, alfaxalone has been reported to cause hypoxaemia in a small number of animals. As stated previously, in a majority of otherwise healthy dogs, changes in \( \text{PaO}_2 \) or extended
periods of post-induction apnoea are probably fairly well tolerated. If a patient is compromised however, these alterations may not be tolerated and the anaesthetist may find the patient decompensates unexpectedly. It is difficult to be able to directly compare many of the published studies due to differences in premedication drugs and dose or speed of administration of alfaxalone. Part of this thesis aims to use consistent methodology to enable direct comparisons of the respiratory effects of alfaxalone and propofol in healthy dogs.

### 2.4 The Respiratory Effects of Propofol

Propofol is a dialkylphenol compound first described as an IV anaesthetic agent in 1977 by Kay and Rolly. Propofol acts in the central nervous system by potentiating the GABA<sub>A</sub> receptor response to endogenous GABA by increasing the probability of the GABA channel to be in the conducting state. Propofol can also directly activate the GABA<sub>A</sub> receptor in a dose-dependent fashion (Hales and Lambert, 1991; Brohan and Basavana, 2017). In spinal neurone studies in mice, propofol potentiated glycine-activated currents, possibly due to significant homology between GABA<sub>A</sub> and glycine receptors. Although this effect is not observed with pentobarbitone or alfaxalone, it may contribute to the anaesthetic effects of propofol (Hales and Lambert, 1991). Propofol also inhibits the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor, the depression of excitatory neurotransmission via this receptor likely contributes to the anaesthetic effects of propofol (Orser et al., 1995). Propofol is the most commonly used IV anaesthetic induction agent in humans and animals due to the favourable anaesthetic profile such as the fast onset and offset, minimal residual sedation and suitability in a variety of patient conditions. As such, there is now a vast amount of literature regarding propofol in humans and animals and this review will focus on papers that describe the respiratory effects of propofol.
The first paper to investigate the use of propofol was published in 1980 and described several experiments in mice, rats, rabbits, cats, pigs, and monkeys. The study was designed to elucidate the effect of propofol in these species compared with thiopentone and Althesin when administered with other adjunct drugs commonly used in anaesthesia such as sedatives and neuromuscular blocking agents (Glen, 1980). In pigs, minimal changes in arterial pH, PaO₂ and PaCO₂ were detected at 3 and 20 minutes after IV injection of propofol. A “short period” of apnoea was detected in mice, rabbits, cats and pigs, and there was one incidence of apnoea in monkeys. At high doses, cyanosis and shallow respiratory patterns were observed in rats. In mice, the effect of some sedative agents appeared to increase the respiratory depression observed with propofol as determined by reduced respiratory frequency, and papaveretum increased the duration of apnoea seen at induction with propofol. The overall conclusion from these experiments was propofol caused some degree of dose-dependent respiratory depression in all species however, the extent of this depression was similar to that seen with thiopentone and Althesin.

Human trials of propofol quickly followed the animal studies and propofol was initially compared with Althesin in 30 people (Rogers et al., 1980). Post-induction apnoea was observed with both drugs in this trial, although the mean duration of apnoea after Althesin (24 ± 4.6 seconds) was significantly shorter than propofol (38 ± 14 seconds). In contrast, a preliminary study comparing Althesin and propofol published by Kay and Stephenson (1980) did not report any incidence of post-induction apnoea with either drug. They did however, observe a transient decrease in respiratory rate in people receiving propofol, compared to no change in rate but an increase in respiratory “depth” in those receiving Althesin. These trials were followed by a dose comparison study by Major et al. (1981). Three doses of propofol (1.5, 2.0 and 2.5 mg kg⁻¹) were compared in 60 patients undergoing minor surgery. Post-induction apnoea occurred in all groups, most frequently in
the highest dose group tested however, in all instances apnoea was less than 30 seconds in duration. While the authors did not directly compare propofol with other IV induction agents, it was stated the incidence of post-induction apnoea following propofol in their study was similar to that seen with other IV induction agents (Major et al., 1981).

Like alfaxalone, propofol was initially suspended in Cremophor ® EL, which caused anaphylactoid reactions in people and animals and in 1984 an emulsion formulation of propofol which did not cause anaphylactoid reactions was released. An induction dose finding study in people was conducted with the new formulation in 1984. Two induction doses were tested (2 mg kg⁻¹ and 2.5 mg kg⁻¹), the authors reported no apnoea in the low dose group, and an incidence of 44% of post-induction apnoea in the high dose group with a mean duration of 53 seconds (Cummings et al., 1984). In comparison, a study designed to assess the effect of three different rates of administration of 2 mg kg⁻¹ propofol (given over 5, 20 or 60 seconds) in people observed apnoea in all groups, with no statistical differences in incidence or duration between the groups (Rolly et al., 1985). Apnoea was defined as lack of spontaneous breathing for 10 seconds or greater in this study, and there was an overall incidence of 85% in the fastest administration group, and 70% in the two slower administration groups (Rolly et al., 1985). The entire 2 mg kg⁻¹ dose of propofol was administered to all patients and this may have impacted on the incidence of apnoea if patients were already anaesthetised but continued to receive propofol. The groups sizes in this study were also small which may be why statistical significance was not detected between the groups.

Another study that investigated the incidence and duration of post-induction apnoea following propofol or thiopentone in premedicated humans found a similarly high incidence of apnoea (Rolly and Versichelen, 1985). People were given a combination of 0.1 mg fentanyl, 5 mg droperidol and 0.5 mg atropine prior to induction of anaesthesia with either
1.5 mg kg\(^{-1}\) or 2 mg kg\(^{-1}\) propofol or 4 mg kg\(^{-1}\) thiopentone. Again, greater than 10 seconds without spontaneous breath was considered post-induction apnoea and this occurred in 6 out of 10 people in the low dose propofol group, and 8 out of 10 people in both other groups. There were no statistically significant differences in incidence or duration of apnoea in any group. The mean duration of apnoea in all groups was close to 30 seconds. In many studies 30 seconds is used as the definition of apnoea and if this definition was applied to the results of this study the incidence of apnoea would significantly decrease in all groups. As previously stated in the discussion on alfaxalone, the differences in definition of post-induction apnoea in the human propofol studies described here makes it difficult at times to directly compare results from different studies.

The ventilatory effects of propofol in comparison to thiopentone in humans was further investigated by Taylor et al. (1986). Patients were premedicated with either atropine alone, or a combination of papaveretum and hyoscine (an antimuscarinic). There was no difference in the incidence of apnoea that lasted 60 seconds or less, but when apnoea lasted longer than 60 seconds the incidence was markedly higher in the propofol group than thiopentone, with the longest period of apnoea being 240 seconds. The respiratory rate in patients given propofol decreased significantly from baseline in the first 1-2 minutes after injection but had returned to baseline by the fourth minute after injection. There was also a greater decrease in minute volume observed in patients receiving propofol compared to thiopentone, and the decrease in minute volume was even more significant in patients receiving papaveretum premedication. This paper was the first to demonstrate more profound respiratory depression in patients receiving opioids and propofol compared to other premedication agents or induction agents. All patients received the same dose of propofol however, so it is possible the opioid premedication reduced the dose requirement of propofol,
which may account for the higher incidence of apnoea observed. There was also a higher incidence of apnoea in patients receiving papaveretum and thiopentone.

The same research group followed up this initial study with a second study that utilised inductance plethysmography to compare the acute ventilatory changes during induction of anaesthesia with thiopentone or propofol in people that were premedicated with papaveretum and hyoscine (Grounds et al., 1987). They found a significant decrease in minute ventilation, tidal volume and mean inspiratory flow in both groups that was maximal between the first and second minutes after injection. There was also a small decrease in respiratory frequency in both propofol and thiopentone groups, however it was not statistically significant. There was a significant decrease in functional residual capacity in patients receiving propofol, compared to a slight increase in the thiopentone group. This study confirmed the earlier work of Taylor et al. (1986) that indicated the ventilatory depression caused by propofol and thiopentone was due to a decrease in tidal volume and respiratory frequency.

The speed at which propofol is administered appears to have an effect on the incidence and duration of post-induction apnoea in humans. Gillies and Lees, (1989) demonstrated that when 2.5 mg kg\(^{-1}\) propofol was administered over 20, 40 or 80 seconds, those in the 80 second group had significantly shorter duration of post-induction apnoea compared to the 20 and 40 second groups, although post-induction apnoea still occurred in 57% of patients. Peacock et al., (1990) also reported an increased incidence of apnoea in elderly humans receiving propofol given to effect by a syringe driver at faster rates (1200 ml hr\(^{-1}\)) compared to slower rates (300 and 600 ml hr\(^{-1}\)). Patients in this study had received fentanyl (a pure \(\mu\) opioid) as premedication, yet the overall incidence of post-induction apnoea was only 18%, much lower than the study by Gillies and Lees, (1989). Peacock et al., (1990) also found the slower rate of administration resulted in a smaller dose of propofol.
required to induce anaesthesia in this population of patients, and a smaller decrease in arterial blood pressure at the end of induction. These results were subsequently replicated in studies by Stokes and Hutton, (1991); Kazama et al., (2000) and Uzun et al., (2011). From these studies in humans, it appears administering propofol more slowly, and to the effect of induction of anaesthesia (as opposed to a pre-calculated dose) conveys the advantage of reducing negative side effects such as post-induction apnoea.

The effect of propofol or thiopentone on hypercapnic ventilatory drive in humans was investigated in 9 healthy male volunteers (Blouin et al., 1991). The subjects breathed two different higher concentrations of CO₂ and breath-by-breath measurements of minute ventilation and P\text{E}CO₂ were recorded. Propofol decreased the slope of the ventilatory response to CO₂ 90 seconds after the administration of propofol and this persisted for at least 20 minutes after administration. This decrease in the slope also occurred with thiopentone however, the effect of propofol was more profound and lasted longer. The same research group then investigated the effect of propofol on the hypoxic ventilatory response in people. Sedative doses of propofol (1 mg kg⁻¹) followed by an infusion were administered and an isocapnic rebreathing technique was used to determine the hypoxic ventilatory response to decreasing SpO₂ from 98% to 70%. Propofol caused the slope of the hypoxic ventilatory response curve to decrease significantly and there was also a decrease in minute ventilation and tidal volume when SpO₂ was at 90% or less. The authors concluded propofol sedation may predispose patients to hypoxia.

Nieuwenhuijs et al., (2001) examined the effect of a sedative concentration of propofol in the blood on the dynamic ventilatory response to CO₂ to determine the respiratory sites of action of propofol. Propofol caused a reduction in central CO₂ sensitivity, however the authors did not detect any change in peripheral CO₂ sensitivity after administration of propofol. There was also a small, but statistically significant, decrease in the apnoeic
threshold (the highest PaCO\textsubscript{2} at which a subject remains apnoeic). The authors concluded from these results that propofol affects the central chemoreflex loop at central receptors, but not the peripheral chemoreflex loop. Jonsson \textit{et al.}, (2005) further elucidated the effect of propofol on carotid body chemosensitivity in an isolated rabbit carotid body preparation. Propofol was found to reduce carotid body chemosensitivity and the magnitude of this depression was dependent on the reduction in oxygen partial pressure. This study also reported that propofol caused a concentration-dependent block of nicotine-induced carotid body chemoreceptor response and this does not appear to be due to activation of the GABA\textsubscript{A} receptor complex (Jonsson \textit{et al.}, 2005).

Preliminary studies of the utility of propofol in animals took place in the 1980’s and the first clinical trial in dogs and cats was published by Hall in 1984. The incidence of post-induction apnoea in 10 dogs and 1 cat anaesthetised with propofol was not reported, however one animal had an arterial blood gas analysis performed during anaesthesia, and the authors reported a normal PaCO\textsubscript{2} (41 mmHg) but low PaO\textsubscript{2} (55 mmHg) (it was not stated if O\textsubscript{2} supplementation was provided). A larger clinical trial from the same research group was conducted with 40 dogs that were premedicated with 0.05 mg kg\textsuperscript{-1} acepromazine and atropine before induction with propofol. They found no incidence of post-induction apnoea lasting longer than 20 seconds (Hall and Chambers, 1987). In contrast, Watkins \textit{et al.}, (1987) reported an incidence of post-induction apnoea of approximately 16% in unpremedicated dogs that received a mean dose of 5.95 mg kg\textsuperscript{-1} of propofol. The authors also suggested the incidence of apnoea could be reduced by administering propofol more slowly. Similar findings were described in a study in 49 cats that found apnoea longer than 30 seconds was common when propofol was administered rapidly, but when only half the calculated dose was administered rapidly and the remainder administered slowly there was no post-induction apnoea (Brearley \textit{et al.}, 1988). Post-induction apnoea was also reported as the most common
adverse effect immediately after induction with propofol in a larger multicentre study involving 207 cats and 290 dogs (Morgan and Legge, 1989). However, even though it was the most common adverse effect, apnoea only occurred in 5 cats and 6 dogs according to the authors, but no time definition of apnoea was provided. The report also did not specify if animals that exhibited post-induction apnoea had received any premedication agents. These early studies were designed to demonstrate the utility of this new anaesthetic agent in dogs and cats so mention of specific respiratory effects was largely lacking. The results of the study by Watkins et al., (1987) and Brearley et al., (1988) suggested there may be an effect of the rate of administration of propofol on post-induction apnoea in dogs and cats.

Propofol continued to gain popularity as an induction agent in small animal anaesthesia leading to more studies evaluating its usefulness both alone and with different premedication drugs. A small study that examined the effect of 4 mg kg\(^{-1}\) propofol given over 20 seconds on cardiorespiratory changes in Beagles that were premedicated with 40 µg kg\(^{-1}\) medetomidine IV reported no change in respiratory frequency in the immediate post-induction period (Vainio, 1991). There was however, a transient decrease in PaO\(_2\) (from 12 ± 2.1 kPa to 10 ± 2.3 kPa) that was significantly lower at 5 minutes after induction and a significant increase in PaCO\(_2\) (from 4.8 ± 0.45 kPa to 6.1 ± 0.35 kPa) with a concurrent decrease in arterial blood pH that persisted for the duration of measurement. Oxygen was not supplemented in these dogs which may have contributed to the lower PaO\(_2\). A pharmacokinetic study of propofol in Greyhounds and mixed-breed dogs also reported no apnoea in any mixed breed dogs, and no apnoea lasting longer than 30 seconds in Greyhounds (Zoran et al., 1993). In contrast, a second study that evaluated the effect of halothane on propofol pharmacokinetics in dogs reported 3 out of 12 dogs in the study had a period of post-induction apnoea (Nolan et al., 1993). The incidence of apnoea reported by Nolan et al., (1993) was similar to the incidence previously reported by Watkins et al., (1987)
and Morgan and Legge, (1989). However, different doses of propofol were used in these two pharmacokinetic studies, 5 mg kg\(^{-1}\) in the study by Zoran et al., (1993) and 6.5 mg kg\(^{-1}\) in the study by Nolan et al., (1993) and this could have influenced the incidence of apnoea.

Bufalari and colleagues, (1996) also reported no incidence of apnoea (in this study apnoea was defined as lack of spontaneous respiration of 60 seconds or longer) in dogs anaesthetised with propofol IV after either no premedication or 10 µg kg\(^{-1}\) medetomidine and 0.02 mg kg\(^{-1}\) atropine IM premedication. Unlike the study reported by Vainio, (1991), Bufalari et al., (1996) found an increase in respiratory frequency in the group receiving propofol only (at a dose of 6.6 mg kg\(^{-1}\) given over 60 seconds) during induction of anaesthesia, which was quickly followed by an insignificant decrease. There was also an insignificant decrease in respiratory frequency in dogs receiving medetomidine and atropine followed by 2.2 mg kg\(^{-1}\) propofol given over 45 seconds. All dogs in this study also demonstrated a decrease in \(\text{SpO}_2\) to less than 90% in the first 5 minutes after induction of anaesthesia and there was an increase in \(P\text{E}_\text{CO}_2\) after administration of propofol, both of these were attributed to the decreased respiratory rate by the authors. The dose and rate of administration of propofol in the studies by Vainio (1991) and Bufalari et al., (1996) were different, the rate of administration in the study by Bufalari et al. was slower, therefore the respiratory results in that study are interesting as one may expect less impact on the respiratory system than the faster administration of propofol as used in the Vainio study.

The effects of propofol administered to hypovolaemic dogs was investigated in 1992 by Ilkiw et al. Propofol (6 mg kg\(^{-1}\) given IV over 30 seconds) was administered to 7 dogs made hypovolaemic by withdrawing blood via an intravenous catheter to maintain a mean arterial blood pressure of 60 mmHg. At three minutes after propofol administration there was a significant decrease in \(\text{PaO}_2\) and arterial blood pH and an increase \(\text{PaCO}_2\). A “short period” of apnoea was also reported, although more specific details were not provided. In the same
year Robertson et al., (1992) reported the cardiopulmonary effects of a propofol infusion in 6 Greyhounds and 7 non-Greyhound dogs. All dogs were given 0.025 mg kg\(^{-1}\) acepromazine and 0.02 mg kg\(^{-1}\) atropine premedication IM before induction of anaesthesia with 3 mg kg\(^{-1}\) propofol given over 60 seconds. One Greyhound was apnoeic for 60 seconds and one was apnoeic for 90 seconds, while only one non-Greyhound had post-induction apnoea, although it persisted for 7 minutes. The Greyhounds also exhibited a statistically significant decrease in respiratory frequency that persisted after the period of post-induction apnoea however, there was no significant change in respiratory frequency in non-Greyhound dogs. As seen in the study by Ilkiw et al., (1992), there was an increase in PaCO\(_2\) in non-Greyhound dogs immediately after induction but it was not clinically significant as this value remained within normal limits (the mean value of PaCO\(_2\) was 41.9 ± 2.2 mm Hg 5 minutes after induction of anaesthesia).

While relatively low incidences of apnoea were reported by Robertson et al., (1992), Smith et al., (1993) reported much higher incidences of dogs experiencing post-induction apnoea when administered 6 mg kg\(^{-1}\) of propofol over 5 seconds after receiving one of four premedication agents (saline, 0.1 mg kg\(^{-1}\) acepromazine IM, 0.2 mg kg\(^{-1}\) diazepam IV or 0.02 mg kg\(^{-1}\) acepromazine and 0.4 mg kg\(^{-1}\) butorphanol IM). In this study apnoea was observed in all 4 groups (10 dogs in each group), only 5 dogs were apnoeic for less than 1 minute, and only 6 dogs out of 40 (3 from the saline group, 2 from the acepromazine group and 1 in the diazepam group) did not have post-induction apnoea. Fifteen dogs were apnoeic for more than 5 minutes, and one dog was apnoeic for 20 minutes. The results of this study did not identify an effect of premedication on the incidence or duration of apnoea. The authors recommended administering propofol more slowly to reduce the possibility of prolonged post-induction apnoea, although this theory was not tested in the study design. The incidence and duration of apnoea reported in the Smith et al. study was much higher than had
previously been observed in dogs. The most likely reason for this is the rapid rate of
administration used in this study, much faster than any studies previously. Acepromazine had
previously been administered with propofol in dogs (Robertson et al., 1992) but this did not
result in the incidence or duration of apnoea reported by Smith et al. however, the effect of
premedication prior to propofol administration on respiratory function requires further
examination.

The following year Cullen and Reynoldson, (1993) reported the effects of 0.8 mg kg^{-1}
xylazine or 30 µg kg^{-1} medetomidine IM as premedication in dogs before induction of
anaesthesia with 3 mg kg^{-1} propofol and compared this to dogs that did not receive any
premedication before induction with 6.55 mg kg^{-1} propofol. A period of apnoea was observed
in all groups. The mean duration was shortest in dogs that received xylazine premedication,
and longest in dogs that received medetomidine premedication. Respiratory frequency did not
change in dogs that received propofol alone, but was significantly decreased in dogs receiving
xylazine or medetomidine 3 minutes after propofol administration. There was also a
significant decrease in PaO₂ and increase in PaCO₂ in all groups, although the medetomidine
group showed the largest decreased in PaO₂ compared to the other two groups (Cullen and
Reynoldson, 1993). Post-induction apnoea was also observed in dogs that received 0.1 mg
kg^{-1} acepromazine IM or 0.2 mg kg^{-1} butorphanol followed by 4.4 mg kg^{-1} propofol IV, or a
combination of acepromazine and butorphanol at those doses followed by 3.3 mg kg^{-1}
propofol IV (Bufalari et al., 1997). Apnoea occurred even when the same dose of propofol
was given at progressively slower rates (over 30, 45 or 60 seconds) The incidence of apnoea
was significantly greater in dogs receiving butorphanol or the combination of butorphanol
and acepromazine, but the SpO₂ decreased below 90% in dogs in all groups. The rate of
administration of propofol also appeared to affect the incidence of apnoea in this study. When
propofol was given over 30 seconds the incidence was 5 out of 6 dogs, when given over 45
seconds it was 4 out of 6 dogs, and when given over 60 seconds it was 1 out of 6 dogs. In all
dogs the Pr CO₂ remained within normal limits throughout the experiment. Dogs that had a
decrease in SpO₂ responded quickly to administration of supplemental oxygen and manual
intermittent positive pressure ventilation (Bufalari et al., 1997). The results of this study
suggested that opioids could increase the respiratory effects of propofol in dogs.

Propofol has also been compared to thiopentone as an induction agent (with no
premedication drugs) in 6 healthy mixed breed dogs and cardiorespiratory variables were
measured for one hour after drug administration (Quandt et al., 1998). Dogs were given 8 mg
kg⁻¹ over 30 seconds and if apnoea persisted for more than 60 seconds, manual ventilation
was started. In all dogs the respiratory frequency decreased immediately after induction, but
then increased from 8-10 minutes after induction. Three dogs had a period of post-induction
apnoea, in 2 dogs it lasted for 2 minutes and in 1 dog it lasted for 4 minutes. All dogs were
administered supplemental oxygen in this study to prevent hypoxaemia. A dose-escalation
study in dogs reported a similar incidence of apnoea (2 out of 4 dogs) when a dose of 6.5 mg
kg⁻¹ was administered (Muir and Gadawski, 1998), although this was of shorter duration than
rate of 20 mg every 10 seconds and found that there was a dose-dependent increase in the
duration of post-induction apnoea when doses greater than 14 mg kg⁻¹ were administered.
The authors attributed the increase in duration of post-induction apnoea to a dose-related
depression of the central inspiratory drive and depression of the ventilatory response to
increasing PaCO₂. The wide variation in duration of apnoea in these studies is possibly due to
the different doses and rates of administration used. As the methodology of administering
propofol is different from one study to another, it is difficult to determine when post-
induction apnoea may be due to the dose of propofol given, the rate at which it was
administered, or the influence of any drugs given prior to induction of anaesthesia.
Clinical trials with propofol continued to evaluate the utility of this anaesthetic induction agent with various combinations of premedication drugs. Lerche et al., (2000) gave dogs undergoing a variety of clinical procedures 0.05 mg kg$^{-1}$ acepromazine and 3 mg kg$^{-1}$ pethidine IM prior to administration of 4 mg kg$^{-1}$ propofol by rapid IV bolus and compared this to dogs given 2 mg kg$^{-1}$ propofol and 2 mg kg$^{-1}$ ketamine. In this study, 6 dogs out of 15 receiving propofol only had post-induction apnoea lasting 60 seconds or longer and 1 dog became cyanotic but did not have apnoea. There was also a significant decrease in respiratory frequency in all groups after induction of anaesthesia. Dogs that received ketamine as well as propofol exhibited exacerbated respiratory depression compared to the propofol only group.

Higher incidences of apnoea were reported by Sano et al., (2003a) and Sano et al., (2003b) in studies that examined the clinical usefulness of propofol in dogs and cats both with and without premedication. In both studies, a dose of 7 mg kg$^{-1}$ propofol was administered over 60 - 90 seconds until it was possible to intubate the trachea. In the first study by this group, all animals were not given any premedication drugs, dogs were administered a mean dose of 6.5 mg kg$^{-1}$ propofol and cats were administered a mean dose of 10.1 mg kg$^{-1}$ over 60-90 seconds. The study did not define what was considered apnoea but did report an incidence of 87% in dogs and 62.5% in cats. The follow up study from this research group compared the effects of premedication with 1000 µg m$^{-2}$ medetomidine IM, 0.1 mg kg$^{-1}$ midazolam and 0.2 mg kg$^{-1}$ butorphanol IV or 0.05 mg kg$^{-1}$ acepromazine and 0.2 mg kg$^{-1}$ butorphanol IM on induction of anaesthesia in dogs with propofol. There was an effect of premedication on induction dose requirements observed, with the lowest mean induction dose (2.2 ± 1.1 mg kg$^{-1}$ propofol) required in the medetomidine group, and the highest dose (3.8 ± 1.0 mg kg$^{-1}$ propofol) required in the acepromazine and butorphanol group. While the doses of propofol required for induction in this study were lower than the previous study by Sano et al., (2003a), there was still a very high incidence of post-induction apnoea in the dogs receiving
midazolam and butorphanol (82.5%), and acepromazine and butorphanol (90%). Dogs that were given medetomidine premedication had an incidence of apnoea of 20% which was significantly less than the other two groups (Sano et al., 2003b). This suggests that the opioid component of the premedication may have contributed to enhancing respiratory depression caused by propofol in these groups however, there were also significant differences in numbers of dogs in each group and this result may have been misleading due to unequal group demographics.

The effect of premedication with acepromazine and morphine, as well as the rate of administration of propofol compared to thiopentone for induction of anaesthesia has also been investigated by Murison, (2001). In this study, 66 dogs were divided equally in to one of 3 groups, all dogs received 0.05 mg kg\(^{-1}\) acepromazine and 0.25 mg kg\(^{-1}\) morphine premedication IM. One group was assigned to receive propofol 4 mg kg\(^{-1}\) as rapidly as possible, one group was assigned propofol 4 mg kg\(^{-1}\) given over 30 seconds, and the final group was assigned thiopentone for induction. In both propofol groups there was a decrease in respiratory frequency in the first minute after induction of anaesthesia which then gradually increased over the next 4 minutes. Post-induction apnoea in this study was defined as lack of spontaneous breathing for 15 seconds or longer. Murison, (2001) reported an incidence of 59% post-induction apnoea in dogs receiving propofol rapidly, 64% were apnoeic and had a longer duration of apnoea when propofol was administered slowly and this difference was considered statistically significant. This is the only study in both humans and animals that suggests administering propofol more quickly results in less post-induction apnoea. However, the same dose of propofol was administered in both groups and it is possible the group administered propofol more slowly actually received more propofol than required to allow tracheal intubation which may have resulted in more post-induction apnoea.
The effect of rate of administration of propofol on induction dose to induce anaesthesia is examined in further detail later in this review.

Target controlled infusion (TCI) of anaesthetic drugs aims to deliver and maintain a specific target blood drug concentration based on population pharmacokinetics (Musk et al., 2005). A study was undertaken to establish a suitable propofol target concentration, out of 4 possible targets (2.5, 3.0, 3.5, and 4.0 µg mL⁻¹), for the induction of anaesthesia in healthy dogs following the administration of 0.03-0.05 mg kg⁻¹ acepromazine and 0.2 mg kg⁻¹ morphine IM. In this study, apnoea was defined as cessation of breathing for 15 seconds or longer. Measurements were made immediately after intubation of the trachea was possible, 3 minutes and 5 minutes after intubation. At time 0 apnoea was observed in all groups and there were no significant differences in incidence between any of the groups. At time 3 minutes however, the incidence in the highest target concentration group was significantly higher than the two lowest target concentration groups, although apnoea was still observed in all 4 groups. At 5 minutes after intubation 40% (8 out of 20) dogs were still apnoeic in the highest target concentration group, there were also 2 dogs in the second highest target concentration group and 1 in the third highest target concentration group (Musk et al., 2005). The dose-dependent incidence of apnoea in this study was similar to that reported by Muir and Gadawski, (1998). The data presentation does not allow for assessment of how quickly propofol was administered and therefore if it had any influence on the incidence of apnoea observed in this study. Bell et al., (2011) also used a TCI device to administer propofol to dogs and compared the effects of intramuscular premedication combinations of 15 µg kg⁻¹ buprenorphine and 0.03 mg kg⁻¹ acepromazine with 15 µg kg⁻¹ buprenorphine and dexmedetomidine at either a low (62.5 µg m⁻²) or high (125 µg m⁻²) dose. The mean blood propofol target to induce anaesthesia in dogs receiving acepromazine and buprenorphine was 2.5 (2.0-3.0) µg mL⁻¹, in dogs receiving low dose dexmedetomidine and buprenorphine was
2.0 (1.5-2.5) µg mL⁻¹, and in dogs receiving high dose dexmedetomidine and buprenorphine was 1.5 (1.0-2.5) µg mL⁻¹. Dogs that received buprenorphine and acepromazine had an incidence of post-induction apnoea of 5%, compared to the low dose dexmedetomidine group where incidence was 16% and an incidence of 25% in the high dose dexmedetomidine group. Further evaluation of the respiratory effects in this study are not possible however, as no other respiratory variables were reported.

Another clinical study that was designed to compare the time to desaturation after induction of anaesthesia between dogs that had been preoxygenated or not also reported a high incidence of post-induction apnoea (McNally et al., 2009). All dogs in this study were premedicated with 0.05 mg kg⁻¹ acepromazine and 0.5 mg kg⁻¹ morphine and were administered 6 mg kg⁻¹ propofol over 7 seconds. All dogs (n = 10) that were preoxygenated before induction of anaesthesia had a period of post-induction apnoea which lasted between 67 and 390 seconds. In dogs that were not preoxygenated (n = 10), 1 dog was not apnoeic after induction, 3 dogs had relatively shorter periods of apnoea up to 77 seconds, and the remaining 16 dogs in the group had periods of apnoea longer than 77 seconds, although the maximum period of apnoea in this group was not reported. PaCO₂ increased in both groups over time after induction. The authors stated the results indicated there was a significant decrease in functional residual capacity (FRC) that started during induction. In contrast to the results of this study, Amengual et al., (2013) reported a lower incidence of apnoea in a clinical study in which dogs were administered 0.03 mg kg⁻¹ acepromazine and 3 mg kg⁻¹ pethidine IM prior to induction of anaesthesia with 3 mg kg⁻¹ propofol given rapidly over 5 seconds. Apnoea occurred in 17 out of 30 dogs receiving propofol, which was similar to the incidence observed in dogs receiving alfaxalone in the same study. There was also an increase in Pt:CO₂ in the first few minutes after induction however the increase was statistically and clinically insignificant. Although the effect of rate of administration was not
evaluated, the authors concluded the apnoea observed in this study was most likely due to the fast rate of administration of propofol.

In the last 20 years, there have also been a number of studies conducted in laboratory conditions that have evaluated propofol in dogs, both with and without premedication. The effect of three different doses of medetomidine (0.4, 4, or 40 µg kg\(^{-1}\) all IV) and three doses of dexmedetomidine (0.2, 2, or 20 µg kg\(^{-1}\) all IV) as premedication prior to induction of anaesthesia with propofol in 6 dogs was reported by Kuusela et al., (2001b). The mean induction dose of propofol was significantly affected by dose of premedication agent, with the highest doses of medetomidine and dexmedetomidine requiring the lowest amount of propofol (0.8-0.9 mg kg\(^{-1}\) compared to 6.0 mg kg\(^{-1}\) in the lowest dose premedication groups). One dog out of 6 dogs exhibited post-induction apnoea in the two lowest dose medetomidine groups and the two highest dexmedetomidine groups, but no dogs in any other group were apnoeic. There was also an increase in PaCO\(_2\) after induction but, as in other studies, this increase was not clinically significant. There was no change in SpO\(_2\) in any groups, although there was a decrease in respiratory frequency in dogs receiving the highest medetomidine dose. Kojima et al., (2002) reported a similar incidence of post-induction apnoea in dogs that were premedicated with a combination of 20 µg kg\(^{-1}\) medetomidine and 0.3 mg kg\(^{-1}\) midazolam before induction with propofol. Dogs that were not premedicated, or were premedicated with 0.05 mg kg\(^{-1}\) acepromazine and 0.2 mg kg\(^{-1}\) butorphanol or 0.1 mg kg\(^{-1}\) midazolam and 0.2 mg kg\(^{-1}\) butorphanol, did not have any post-induction apnoea. There was also a decrease in respiratory rate in dogs receiving medetomidine and midazolam and midazolam and butorphanol. A significant increase in PaCO\(_2\) was noted in dogs receiving acepromazine and butorphanol, while a decrease in PaO\(_2\) was seen in dogs receiving medetomidine and midazolam, acepromazine and butorphanol, and midazolam and butorphanol. In addition, a significant decrease in SpO\(_2\) was observed in all three
premedication groups. Oxygen supplementation was not provided in this study, which may account for the decrease in PaO₂. In this study, propofol was administered at 1/4 - 1/3 of the calculated dose given at 1 ml per 10 seconds, with a pause of 15-20 seconds before continuing to administer propofol so that the total dose required to allow tracheal intubation was administered over longer than 60 seconds. The mean induction doses of propofol for the premedication groups ranged from 2.7 mg kg⁻¹ to 4.9 mg kg⁻¹ and in dogs that did not receive premedication the mean induction dose was 6.5 mg kg⁻¹. The authors attributed the low incidence of apnoea and mild respiratory effects to the slow administration of propofol compared to other studies (Kojima et al., 2002).

The cardiopulmonary effects of propofol has been compared to etomidate in laboratory Beagles following intravenous midazolam (0.3 mg kg⁻¹) (Sams et al., 2008). Midazolam was administered at least 1 minute prior to induction of anaesthesia with propofol. The induction dose of propofol was administered at 10% of the total calculated volume (8 mg kg⁻¹) given every 6 seconds until tracheal intubation was possible. Three out of 9 dogs that received propofol had an unspecified period of post-induction apnoea however, there was no change in PaCO₂ in this group. There was also a decrease in PaO₂ from baseline to immediately after induction from 96 mmHg to 53 mmHg. The authors did not state this was a significant difference, however clinically this would be an important decrease, particularly if oxygen is not supplemented, as in this study. In comparison, Ambros et al., (2008) reported a laboratory study in six dogs that were premedicated with 0.02 mg kg⁻¹ acepromazine and 0.05 mg kg⁻¹ hydromorphone IV before administration of 4 mg kg⁻¹ propofol given over 60 seconds and this was compared to alfaxalone. One out of 6 dogs receiving propofol had post-induction apnoea, this incidence was similar to that reported by Bufalari et al., (1997) and Kuusela et al., (2001b). A significant decrease in arterial blood pH and increase in PaCO₂ were detected 5 minutes after induction with propofol, there was also
a decrease in respiratory frequency however this was not statistically significant. The incidence of apnoea in dogs that received alfaxalone in this study was similar to the propofol group and the authors stated there was no difference between the two groups with regards to degree of respiratory depression.

In contrast, when six dogs were premedicated with 40 µg kg\(^{-1}\) medetomidine IM followed by induction of anaesthesia with 1 mg kg\(^{-1}\) propofol IV, there was no change in minute volume of respiration but there was an increase in PaCO\(_2\) after induction however, no post-induction apnoea was detected (Seliskar et al., 2007). Similarly, when six dogs were premedicated with 10 µg kg\(^{-1}\) medetomidine and 0.05 mg kg\(^{-1}\) hydromorphone IV before induction of anaesthesia with 1 mg kg\(^{-1}\) propofol, an increase in PaCO\(_2\) was detected after induction of anaesthesia, but again there was no incidence of post-induction apnoea (Enouri et al., 2008). The doses of propofol in these two studies are much lower than previous studies in dogs and is the most likely reason post-induction apnoea was not observed in both studies. The small sample sizes and the use of dogs acclimated and/or bred in laboratory conditions in both studies limit the ability to extrapolate the results of these studies to a more heterogeneous canine population and clinical environment.

Another laboratory study in six dogs used a dose escalation method to compare the respiratory effects of alfaxalone and propofol (Keates and Whittem, 2012). Each drug was administered to each dog at the labelled dose (6.5 mg kg\(^{-1}\) propofol), and then at increasing multiples of the labelled dose (2x, 3x, 10x, and 20x) until the dog became apnoeic after induction, at which point it was removed from the study and did not receive any further doses of the induction agent. Apnoea in this study was defined as cessation of breathing for 60 seconds or longer. The rate of administration was to give \(\frac{1}{4}\) of the total dose every 15 seconds, therefore as the doses were increased, the rate of administration of propofol also increased. Dogs that received 6.5 mg kg\(^{-1}\) of propofol did not have any apnoea, 2 out of 6
dogs became apnoeic when given 13.5 mg kg\(^{-1}\) (2x labelled dose) and all remaining dogs had apnoea when given 32.5 mg kg\(^{-1}\) of propofol. Dogs that received alfaxalone also became apnoeic, however one dog did not become apnoeic until 20x the labelled dose was administered. Based on this result, the authors concluded that propofol has a narrower safety margin for respiratory function than alfaxalone. However, the sample size in this study was extremely small, and the rate of administration of both drugs increased with increasing doses. As previously discussed, more rapid rate of administration can result in increased incidence of post-induction apnoea so this method may have influenced the results observed when propofol was used.

Henao-Guerrero and Ricco, (2014) compared the cardiorespiratory effects of propofol with that of propofol-ketamine and ketamine-diazepam combinations in 10 healthy Beagles. All dogs were premedicated with 0.02 mg kg\(^{-1}\) acepromazine and 0.05 mg kg\(^{-1}\) oxymorphone IV before administration of 4 mg kg\(^{-1}\) propofol over 60 seconds. The authors reported that all induction drugs caused some post-induction apnoea ranging in duration from 20 seconds to no more than 60 seconds and there was no difference between the groups. The PaO\(_2\) decreased to less than 80 mmHg in all groups after induction (despite tracheal intubation of all dogs and provision of 100% O\(_2\)), however there was a clinically insignificant increase in PaCO\(_2\). This effect was attributed to ventilation-perfusion mismatch. In comparison, Suarez et al., (2012) did not observe any post-induction apnoea in healthy dogs given 0.01 mg kg\(^{-1}\) acepromazine and 0.4 mg kg\(^{-1}\) morphine IM premedication and induced with a mean dose of 5.8 ± 0.3 mg kg\(^{-1}\) of propofol IV. In this study, propofol was administered over approximately 40 seconds and was given until it was possible to intubate the trachea. The duration of cessation of spontaneous breathing was not defined in this paper however, and it is possible that periods of apnoea did occur in these dogs but were not considered clinically important by the authors.
Post-induction apnoea was observed in a study designed to evaluate the effect of body condition score of dogs on the induction dose requirement of propofol (Boveri et al., 2013). All dogs were premedicated with 5 µg kg\(^{-1}\) medetomidine and 0.2 mg kg\(^{-1}\) butorphanol IM before administration of propofol via a syringe driver set at a rate of 1.5 mg kg\(^{-1}\) minute\(^{-1}\). In dogs considered “Normal weight” there was an incidence of post-induction apnoea of 15 seconds or more in 11 out of 25 dogs, and in the “Overweight” dogs there was an incidence of apnoea of 3 out of 21, although this was not statistically significant (p = 0.052). This study did find a significant difference in propofol induction dose requirement between the two groups, dogs in the “Normal Weight” group required 2.24 mg kg\(^{-1}\), compared to 1.83 mg kg\(^{-1}\) in the “Overweight” group. This difference in induction dose may have influenced the incidence of apnoea observed. The incidence of apnoea in the “Normal weight” group was the same as the incidence of apnoea detected by Okushima et al., (2015) in 25 dogs administered 7 µg kg\(^{-1}\) fentanyl IV as a co-induction agent with propofol (mean dose 2.15 ± 0.59 mg kg\(^{-1}\)) administered “slowly to effect”. Canfrán et al., (2016) also found post-induction apnoea occurred in 4 out of 7 dogs administered a mean induction dose of 2.9 ± 0.9 mg kg\(^{-1}\) propofol following premedication with 5 µg kg\(^{-1}\) dexmedetomidine. Dogs were also administered premedication combinations of 5 µg kg\(^{-1}\) dexmedetomidine and 0.3 mg kg\(^{-1}\) midazolam, 5 µg kg\(^{-1}\) dexmedetomidine and 0.3 mg kg\(^{-1}\) methadone, and 5 µg kg\(^{-1}\) dexmedetomidine, 0.3 mg kg\(^{-1}\) midazolam and 0.3 mg kg\(^{-1}\) methadone in this study. While the induction dose of propofol was significantly lower in all three groups (ranging between 0.9 and 1.5 mg kg\(^{-1}\)) compared to the group that only received dexmedetomidine, there was no significant difference in the incidence of apnoea in all 4 groups (2 dogs out of 7 in both the dexmedetomidine-midazolam and dexmedetomidine-methadone-midazolam groups, and 4 dogs out of 7 in the dexmedetomidine-methadone group were apnoeic). This may be due to
the effect of combining additional drugs that can influence respiratory function with
dexmedetomidine that could have overcome the effect of a lower dose of propofol.

The effect of the rate of administration of propofol has been investigated in sheep and
rats. In a physiological model of induction of anaesthesia in sheep two dose regimens were
tested, administering a bolus of 200 mg propofol over 20 seconds or administering an
infusion of propofol at a rate of 40 mg min\(^{-1}\) for 5 minutes. It was found that the maximum
depth of anaesthesia occurred between 2 and 3 minutes after administration of propofol
regardless of method of administration (i.e. bolus vs. infusion) (Ludbrook and Upton, 1997).
More rapid injection of propofol did not speed up induction of anaesthesia however, the dose
requirements were higher with rapid injection. Injecting propofol over 2 minutes minimised
the dose required to achieve induction of anaesthesia. The research group attempted to
identify the mechanism that allowed slower administration and lower doses of propofol to
achieve anaesthesia in a second study. In this follow up study however, the authors found the
dose-sparing observed with slow administration was related only to improved titration to
effect and did not result in more anaesthesia for a given dose (Ludbrook et al., 1998).
Another study in sheep compared the effect of two different rates of administration, a single
dose (200 mg IV) given rapidly, or the same dose given over 2 minutes. The effect on
respiratory rate or incidence of apnoea was not reported, there was a transient decrease in
\(\text{PaO}_2\) and increase in \(\text{PaCO}_2\) but there was no difference in the degree of respiratory
depression as measured by these variables between the two rates of administration (Zheng et
al., 1998). The effect of rate of administration of propofol has also been investigated in rats
(Jang et al., 2009). This study compared a dose of 20 mg kg\(^{-1}\) propofol administered over 1, 2
or 3 minutes to determine the cardiopulmonary and anaesthetic effects. One rat out of 7 had
post-induction apnoea when propofol was administered at the fastest rate, no rats in either of
the other groups had apnoea. Rats in the fastest rate group also had the most severe decrease
in respiratory frequency, particularly compared to the slowest group. The authors concluded that administering propofol more slowly resulted in less cardiopulmonary depression in rats than fast administration, while also producing a deeper and longer lasting anaesthesia.

Propofol clearly has a significant effect on the respiratory system in many species. The extent of respiratory depression caused by propofol appears to be related to both the dose administered and the rate of administration of that dose. The effect of additional drugs administered concurrently with propofol appears to vary and further research is required in order to elucidate the extent to which adjunct anaesthetic drugs influence respiratory depression with propofol. This thesis will attempt to identify some specific effects of adjunct drugs and the rate of administration of propofol on the incidence and duration of post-induction apnoea in healthy dogs.
Chapter 3: Post-induction apnoea in dogs premedicated with acepromazine or dexmedetomidine and anaesthetised with alfaxalone or propofol

3.1 Introduction

Many anaesthetic agents can cause ventilatory depression, the extreme example of which is apnoea. Induction of general anaesthesia frequently causes a period of apnoea commonly referred to as post-induction apnoea, the occurrence of which does not appear to be related to the depth of anaesthesia (Haskins, 2015). Apnoea is considered a serious adverse event of anaesthesia as it can result in hypoxaemia, respiratory acidosis and ultimately death if left untreated (Wilson and Shih, 2015). In addition, post-induction apnoea can compromise the transition from intravenous induction to anaesthetic maintenance by a volatile agent as a result of reduced uptake of inspired gases (Keates and Whittem, 2012).

Propofol (a phenol compound) and alfaxalone (a neuroactive steroid) are intravenous anaesthetic agents that interact with the gamma aminobutyric acid (GABA) receptor to enhance the inhibitory action of endogenous GABA and are commonly used in small animal anaesthesia (Amengual et al., 2013). Propofol and alfaxalone are characterised by rapid and smooth induction of general anaesthesia (Maney et al., 2013), although both drugs exhibit dose-dependent cardiorespiratory depressive properties (Muir and Gadawski, 1998; Muir et al., 2008). Post-induction apnoea following administration of propofol has been well-documented in both human (Stokes and Hutton, 1991) and animal studies (Taylor et al., 1986; Muir and Gadawski, 1998; Muir et al., 2009; Amengual et al., 2013). However, there are contradictory reports regarding the incidence of post-induction apnoea following alfaxalone administration in dogs and cats (Ambros et al., 2008; Muir et al., 2008; Martinez Taboada and Murison, 2010; Keates and Whittem, 2012; Maney et al., 2013).
Acepromazine and dexmedetomidine are frequently used to provide tranquilisation or sedation in dogs. Acepromazine is a phenothiazine compound that exerts anti-dopaminergic effects in the central nervous system leading to sedation, while dexmedetomidine is an alpha-2 (α2)-adrenergic receptor agonist and causes sedation primarily by binding to α2-receptors in the CNS (Correa-Sales et al., 1992). Methadone is a pure μ opioid receptor agonist used for analgesia and sedation in dogs. Methadone acts synergistically with both acepromazine (Monteiro et al., 2008) and dexmedetomidine (Canfrán et al., 2016) to produce more profound sedation when used with either of these drugs. Dexmedetomidine and methadone can cause depression of ventilatory drive (Canfrán et al., 2016), whereas acepromazine typically has little or no effect on respiration (Popovic et al., 1972). The impact of the combination of acepromazine and methadone or dexmedetomidine and methadone premedicants on post-induction apnoea following either propofol or alfaxalone induction has not previously been directly compared.

The aim of this study was to evaluate the influence of the choice of premedication combination (methadone with acepromazine or dexmedetomidine) and the choice of induction agent (propofol or alfaxalone) on the incidence and duration of post-induction apnoea in healthy dogs. Based on our clinical impressions, the hypothesis of this study was that the incidence and duration of post-induction apnoea would be greater when methadone and dexmedetomidine were given for premedication and alfaxalone was used as the induction agent when compared to propofol. A second hypothesis was that dogs premedicated with acepromazine and methadone would have a lower incidence and shorter duration of post-induction apnoea than those treated with dexmedetomidine and methadone, regardless of choice of induction agent.

3.2 Materials and methods
3.2.1 Animals

This study was approved by the University of Melbourne Animal Ethics Committee (Ethics ID: 1413315.4) and informed written owner consent was obtained prior to enrolment. Dogs scheduled to undergo elective neutering procedures were recruited into the study if they were over 4 months of age, and were assessed as American Society of Anesthesiologists (ASA) physical status classification 1 or 2. Exclusion criteria included cardiorespiratory abnormalities detected on physical examination, abnormal packed red cell volume or total solids, brachycephalic conformation, or patients receiving medications with known sedative effects such as phenobarbital, benzodiazepines, gabapentin, tramadol or other opioids.

3.2.2 Study Protocol

All dogs were admitted to hospital on the morning of the study. Owners were instructed to withhold food for at least eight hours but to allow access to water ad libitum on the night before admission. Dogs were randomly allocated to one of four protocol groups (MA+A, MA+P, MD+A, or MD+P) using computer generated random numbers (Microsoft Excel 2010; Microsoft Corp. WA, USA). Dogs were administered intramuscular (IM) premedication with MA (methadone 0.5 mg kg\(^{-1}\) (Methone, Ceva Animal Health, Glenorie, NSW, Australia) + acepromazine 0.05 mg kg\(^{-1}\) (ACP 2, Ceva Animal Health, Glenorie, NSW, Australia)) or MD (methadone 0.5 mg kg\(^{-1}\) + dexmedetomidine 5 µg kg\(^{-1}\) (Dexdomitor, Zoetis, NSW, Australia)). Induction of anaesthesia was achieved by intravenous (IV) administration of alfaxalone (A) (Alfaxan, Jurox, Australia) at a rate of 2 mg kg\(^{-1}\) minute\(^{-1}\) or with IV propofol (P) (Provive 1%, Claris Lifesciences, NSW, Australia) at a rate of 4 mg kg\(^{-1}\) minute\(^{-1}\). A physical examination was performed and baseline respiratory rate (\(f_R\)), heart rate (HR) and temperature were recorded. All dogs were premedicated in the cervical muscles. Approximately 15 minutes after premedication a 20 gauge or 22 gauge catheter was placed in a cephalic vein. Thirty minutes after premedication the post-premedication \(f_R\), HR and
temperature were recorded and degree of sedation was assessed by an observer trained in the use of the sedation scoring scale. The degree of sedation was assessed and scored by the same observer (SEB) using a previously published scale ranging from -10 (not sedated) to 14 (profound sedation) (Hofmeister et al., 2010) (Appendix S1).

At the completion of the assessment of sedation all dogs were then preoxygenated for 5 minutes via a face mask attached to an appropriately sized circle rebreathing system with oxygen (O₂) at 4 L minute⁻¹. Baseline oxygen saturation of haemoglobin (SpO₂) and HR were measured continuously during the preoxygenation phase using a multiparametric monitor (SurgiVet CDS 2000, Smiths Medical PM Inc. WI, USA) with the probe placed on the upper lip or tongue of the dog. Respiratory rate was also measured via observation of chest excursions prior to induction. Induction of anaesthesia and endotracheal intubation were conducted by the same experienced anaesthetist (SEB) in all cases. Anaesthesia was induced in all dogs by delivering the protocol agent IV via the cephalic catheter at the previously described rate of administration via a syringe driver using an appropriately sized device-compatible syringe (Baxter Flo-Gard GSP Syringe Pump, Baxter Healthcare Pty Ltd, Australia) until orotracheal intubation could be achieved. In order to minimise bias on the part of the unblinded anaesthetist performing the orotracheal intubation, a standardised methodology was followed. The anaesthetist observed that the dog was unable to support its head at which time they assessed the jaw tone. If the jaw tone was minimal to absent and no resistance was met when gentle traction was applied to the tongue, orotracheal intubation was attempted. If the jaw tone was sufficient to prevent intubation, the anaesthetist allowed 10 seconds to elapse before testing the jaw tone again. If the animal coughed or resistance to passing the endotracheal tube (ETT) was met, the process was halted for 10 seconds before attempting intubation again. Immediately upon successful orotracheal intubation, the induction agent infusion was stopped, the ETT was connected to the rebreathing system and
delivery of isoflurane (Isoflo, Abbott Australia) was initiated with a vaporiser setting of 2% in O_2 at a flow rate of 2 L minute^{-1}. The ETT cuff was inflated after the breathing circuit was connected using pressure change in the pilot balloon as a guide. A positive pressure breath-hold leak test of the ETT cuff was performed after ventilation resumed.

An additional anaesthetist (JEC) monitored respiration from the time of starting the infusion of induction agent and recorded the occurrence and duration of post-induction apnoea. Apnoea was defined as cessation of breathing for a period of 30 seconds or greater. The HR and SpO_2 were monitored throughout induction of anaesthesia and the apnoeic period using the same monitor and probe position as previously described. The period of apnoea ended when spontaneous breathing returned. If SpO_2 decreased below 90% the anaesthetist intervened and started intermittent positive pressure ventilation (IPPV) by administering a positive pressure breath to 12-15 cm H_2O using the rebreathing bag every 15 seconds until SpO_2 increased to at least 95% and spontaneous ventilation had resumed.

Post-induction measurements of SpO_2, end tidal partial pressure of carbon dioxide (P_{E\cdot CO_2}), oscillometric blood pressure (systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressure), and lead II electrocardiogram (ECG) were recorded one minute after the first spontaneous breath was observed after orotracheal intubation, or upon initiation of IPPV if the SpO_2 decreased below 90%. If apnoea occurred, HR and SpO_2 were monitored and recorded throughout the apnoeic period however the remainder of the monitoring devices were not attached to the dog until after the first spontaneous breath in order to prevent any unnecessary stimuli that might influence ventilatory drive. From the time of the first spontaneous breath (post-induction time point) onwards the HR, f_R, SpO_2, P_{E\cdot CO_2}, SAP, DAP, and MAP were monitored and recorded every five minutes. Body temperature was monitored and recorded every 15 minutes during the surgical procedure via an oesophageal temperature probe. In addition, all dogs received lactated Ringer’s solution (Compound
sodium lactate, Fresenius Kabi, Australia) IV at a rate of 10 mL kg\(^{-1}\) hour\(^{-1}\) for the duration of
anaesthesia.

Hypotension, defined as MAP less than 60 mmHg, was treated by decreasing the
isoflurane vaporiser setting by 0.5% every 5 minutes, administering 10 mL kg\(^{-1}\) of LRS IV
over 10 minutes or by dopamine (Dopamine hydrochloride; Hospira, Australia) infusion IV
started at 7 µg kg\(^{-1}\) minute\(^{-1}\) and adjusted based on blood pressure response as deemed
appropriate by the anaesthetist until MAP increased above 60 mmHg. Manual IPPV was
provided during anaesthesia after the initial induction phase if \(P_{\text{a}}\)\text{'}CO\(_2\) increased above 60
mmHg. All dogs received 0.2 mg kg\(^{-1}\) meloxicam (Metacam, Boehringer Ingelheim,
Australia) subcutaneously at the end of anaesthesia.

3.2.3 Statistical analysis

Prospective power analysis (IBM SPSS Sample Power 3, SPSS Inc., USA) of the
independent group design to evaluate the influence of premedication or induction agent
choice indicated a minimum of 30 animals were required to achieve 95% accuracy. The
analysis indicated 15 dogs would be required to represent each premedication combination
and 15 dogs to represent each induction agent to provide sufficient power to detect a 15%
difference in the incidence or mean duration of apnoea with a study power of 80% and alpha
value of 0.05. A difference of 15% was arbitrarily selected as it was believed to represent a
reasonable choice providing adequate clinical difference (10 seconds for each minute of
apnoea with a standard deviation of 0.45 seconds) without excessively compromising on
specificity. Data were tested for normality using the Ryan-Joiner test. Sedation scores were
analysed with 2-sample T tests and proportion of dogs panting and incidence of apnoea was
analysed by Fisher’s exact test. General linear regression models were used to evaluate the
differences between premedication combinations, induction agents, or both premedication
and induction agent together, while accounting for the influence of sedation score. Where
significant differences were found, a Sidak test for post-hoc analysis with significance set at \( p < 0.05 \) was performed. The non-parametric data sets of weight, gender and age were analysed with the Kruskal-Wallis test. Analysis was performed using Minitab 17 Statistical Software (Minitab Inc., PA, USA) and GraphPad Prism 6 for Windows (GraphPad Software Inc., CA, USA). Results are presented as mean ± standard deviation or median (range) as appropriate.

3.3 Results

Thirty-two client-owned dogs were enrolled, with 8 dogs in each group. The dogs were of various breeds, between 4 months and 4 years of age, weighing between 3 and 40 kg. The groups were not significantly different in terms of age \([7 (4–46) \text{ months}, p = 0.42]\), gender \((15 \text{ females, } 17 \text{ males, } p = 0.727)\), or body weight \([10 (3–46) \text{ kg, } p = 0.87]\). Groups MA+A and MA+P had significantly lower sedation scores than groups MD+A and MD+P \((p \leq 0.001)\). There was no difference in sedation scores between MA+A and MA+P \((p = 0.236)\), nor between MD+A and MD+P \((p = 0.212)\) (Table 1). All dogs were adequately sedated for catheter placement. There was no difference in mean induction dose between A groups or between P groups and the overall mean induction dose of alfaxalone and propofol was \(2.2 \pm 0.6 \text{ mg kg}^{-1}\) and \(4.6 \pm 0.9 \text{ mg kg}^{-1}\) respectively (Table 1). No dogs exhibited excitement or myoclonus during induction.

Analysis of the incidence of apnoea in each group revealed there were no statistically significant differences between any of the groups either when premedication choice \((p = 0.693)\), induction drug choice \((p = 0.693)\) or the combination of premedication and induction drug choice \((p = 0.266)\) were considered (Table 1). The overall incidence of apnoea in A groups was 11 of 16 dogs and in P groups was 12 of 16. The mean duration of apnoea was also not different between groups when the effect of premedication \((p = 0.551)\), the effect of induction drug \((p = 0.883)\), or the combination of premedication and induction drug were
considered \((p = 0.895)\) (Table 1). The mean duration of apnoea in A groups was 125 ± 113 seconds and in P groups was 119 ± 109 seconds.

**Table 1** Mean ± SD values for sedation scores, induction dose, incidence, and duration of apnoea in dogs after intramuscular premedication with MA (methadone 0.5 mg kg\(^{-1}\) + acepromazine 0.05 mg kg\(^{-1}\)) or MD (methadone 0.5 mg kg\(^{-1}\) + dexmedetomidine 5 µg kg\(^{-1}\)) and intravenous induction of anaesthesia with alfaxalone (A) or propofol (P).

<table>
<thead>
<tr>
<th>Group</th>
<th>Sedation Score (maximum 14)</th>
<th>Induction Dose (mg kg(^{-1}))</th>
<th>Incidence of Apnoea (%)</th>
<th>Duration of Apnoea (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MA+A</td>
<td>6 ± 3*</td>
<td>2.3 ± 0.6</td>
<td>75.0</td>
<td>110 ± 82</td>
</tr>
<tr>
<td>MA+P</td>
<td>8 ± 4*</td>
<td>4.7 ± 0.9</td>
<td>62.5</td>
<td>109 ± 103</td>
</tr>
<tr>
<td>MD+A</td>
<td>13 ± 3\†</td>
<td>2.1 ± 0.6</td>
<td>62.5</td>
<td>140 ± 129</td>
</tr>
<tr>
<td>MD+P</td>
<td>11 ± 3\†</td>
<td>4.4 ± 0.9</td>
<td>87.5</td>
<td>128 ± 107</td>
</tr>
</tbody>
</table>

*Sedation score: Range -10 (no sedation) to 14 (profound sedation), \*scores are the same but significantly lower than \(\dagger\) \((p \leq 0.001)\); \(\dagger\)scores are the same. No significant differences between induction doses of alfaxalone \((p = 0.468)\) or propofol \((p = 0.508)\).*
Respiratory rates are shown in Figure 1. Panting was a common finding after premedication and was standardised to a value of 100 breaths minute\(^{-1}\) for the purpose of statistical analysis. Four dogs in MA+A, 2 dogs in MA+P and 1 dog each in both MD groups were recorded as panting post-premedication. There was no statistically significant difference in number of dogs panting between groups post-premedication \((p = 0.262)\). Group MA+P had a significantly higher \(f_R\) post-premedication compared to groups MD+A and MD+P \((p = 0.01\) and \(p = 0.014\) respectively), but there were no differences in \(f_R\) between groups MD+A, MD+P and MA+A or between groups MA+A and MA+P. There was a significant decrease in \(f_R\) in all groups from baseline \(f_R\) to post-induction \(f_R\) \((p \leq 0.001)\). The temperature of all dogs at baseline was 38.8 ± 0.4 degrees Celsius (ºC) and post-premedication was 38.3 ± 0.6 ºC, there were no differences in temperature between groups.

Group MA+A had lower \(P_e\)\(^{'}\)CO\(_2\) post-induction at the next two 5 minute observation points (at 6 and 11 minutes after the first spontaneous breath) compared to Group MD+A, but not when compared to Groups MA+P and MD+P \((p = 0.02\) and \(p = 0.04\)). The \(P_e\)\(^{'}\)CO\(_2\) was not significantly different between groups at any other time in the first 20 minutes of observation after induction of anaesthesia (Figure 2). There were no statistically significant differences in SpO\(_2\) between groups either post-premedication or at any time in the first 20 minutes post-induction. One dog in the MD+P group desaturated after 70 seconds of apnoea. Intermittent positive pressure ventilation was initiated immediately and SpO\(_2\) increased to 95% within 60 seconds.
Figure 1 Respiratory rate (fR) (mean ± SD) at baseline, 30 minutes after premedication (post-premedication) and 1 minute after first spontaneous breath (post-induction) in dogs after intramuscular premedication with MA (methadone 0.5 mg kg\(^{-1}\) + acepromazine 0.05 mg kg\(^{-1}\)) or MD (methadone 0.5 mg kg\(^{-1}\) + dexmedetomidine 5 µg kg\(^{-1}\)) and intravenous induction of anaesthesia with alfaxalone (A) or propofol (P). * Indicates MA+P significantly higher than MD+A (p = 0.01), † indicates MA+P is significantly higher than MD+A (p = 0.014), ‡ indicates all groups significantly lower than baseline (p ≤ 0.001).
Figure 2 End tidal partial pressure of carbon dioxide (PₐCO₂) (mean ± SD) after the first spontaneous breath in dogs following intramuscular premedication with MA (methadone 0.5 mg kg⁻¹ + acepromazine 0.05 mg kg⁻¹) or MD (methadone 0.5 mg kg⁻¹ + dexmedetomidine 5 µg kg⁻¹) and intravenous induction of anaesthesia with alfaxalone (A) or propofol (P).

*MA+A had lower PₐCO₂ at 6 and 11 minutes compared to MD+A (p = 0.02 and p = 0.04 respectively).
3.4 Discussion

The aim of this study was to evaluate the influence of the choice of commonly used IM premedication combinations (methadone with acepromazine or dexmedetomidine) and the choice of IV induction agent (propofol or alfaxalone) on the incidence and duration of post-induction apnoea in healthy dogs.

The results of this study suggest the induction of anaesthesia with propofol or alfaxalone IV following IM premedication with methadone and acepromazine or dexmedetomidine is likely to cause post-induction apnoea of similar duration. The incidence of apnoea in this study is slightly higher than the incidence of apnoea reported by Amengual et al., (2013) and Okushima et al., (2015). The doses of acepromazine and opioid used in the current study were higher than those used by Amengual et al., (2013), while no tranquiliser or sedative agent was used in the study by Okushima et al., (2015). In contrast to the current study, Keates and Whittem (2012) found post-induction apnoea was more likely to occur following propofol induction than alfaxalone in a dose-escalation study where no premedication was given. Maney et al. (2013) did not report any incidence of apnoea following either 8 mg kg\(^{-1}\) propofol or 4 mg kg\(^{-1}\) alfaxalone IV with no premedications. The protocol in the current study was designed to reflect a clinical setting where balanced anaesthetic techniques are employed to provide neuroleptanalgesia. The use of premedication agents and the level of sedation achieved in this study may have contributed to the higher incidence of post-induction apnoea observed compared to studies examining the effect of the induction agents alone (Keates and Whittem, 2012; Maney et al., 2013) or those using lower doses of premedication agents (Amengual et al., 2013; Okushima et al., 2015).

Acepromazine, at the dose used in this study, decreases respiratory rate in dogs however there is a corresponding increase in tidal volume. As a result there are no changes in
arterial partial pressure of oxygen \((\text{PaO}_2)\) or arterial partial pressure of carbon dioxide \((\text{PaCO}_2)\) (Popovic et al., 1972). Alpha-2 agonists decrease respiratory centre sensitivity (Lerche and Muir, 2004) and blunt the neurorespiratory drive response to increased \(\text{PaCO}_2\) (Sabbe et al., 1994). Given the central effects on ventilatory drive of \(\alpha_2\) receptor agonists, it might be reasonable to expect greater duration and/or higher incidence of post-induction apnoea following dexmedetomidine administration. However, this was not observed in this study. It is possible that acepromazine and opioids have a greater synergistic effect on ventilation than was anticipated or the dose of dexmedetomidine used in this study affected ventilatory drive less than expected.

The lack of difference between the premedication combinations in this study is consistent with the findings of Herbert et al. (2013) where no difference in incidence of apnoea was seen in dogs premedicated with a combination of dexmedetomidine or acepromazine and buprenorphine undergoing alfaxalone total intravenous anaesthesia. Methadone, a pure \(\mu\) opioid agonist, can contribute to reduced ventilatory response to increasing hypercapnia when used with other injectable anaesthetic drugs (Stuth et al., 2012). All dogs in this study received methadone so the influence of methadone on ventilatory depression in these animals would be expected to be similar within each group. Further studies are required to elucidate any differences in the effect of combining acepromazine or dexmedetomidine with methadone on ventilatory drive in dogs.

Changes in \(f_R\) from baseline to post-induction were similar among acepromazine and dexmedetomidine groups and all groups showed significantly lower \(f_R\) post-induction. The \(f_R\) of MA+P was higher post-premedication than the dexmedetomidine groups, although it was not statistically different than the MA+A group. The higher \(f_R\) observed in group MA+P after premedication is possibly the result of a higher, though not statistically significant, proportion of dogs recorded as panting compared to the other groups. Body temperature in all dogs post-
premedication was within clinically normal limits; therefore, panting was unlikely due to high body temperature. Arterial blood gas analysis was not performed in this study making it impossible to accurately assess the extent of respiratory depression caused after premedication with these drugs.

There were no statistically significant differences in SpO\textsubscript{2} between groups either after premedication or at any time in the first 20 minutes post-induction. One dog in the MD+P group desaturated after 70 seconds of apnoea, however this dog responded well to IPPV. All dogs in the study were preoxygenated for 5 minutes prior to induction in an effort to prevent desaturation in patients that would become apnoeic after induction of anaesthesia. McNally \textit{et al.}, (2009) reported preoxygenation for 3 minutes increased the time to desaturation (approximately 300 versus 70 seconds) compared to dogs breathing room air when sedated with acepromazine and morphine and induced with propofol. Apnoea causes reduced alveolar ventilation, most likely leading to the decrease in SpO\textsubscript{2} observed in this dog. This supposition is supported by the almost immediate increase in SpO\textsubscript{2} in response to IPPV. Other possible causes could have been peripheral vasoconstriction due to dexmedetomidine or compression of the vessels in the tongue by the probe resulting in poor blood flow and therefore an erroneous SpO\textsubscript{2} reading, or equipment malfunction such as interference causing an error in the probe reading.

Despite the statistically significant difference in sedation between dogs receiving acepromazine and dogs receiving dexmedetomidine there was no difference in the induction dose of propofol or alfaxalone required to allow endotracheal intubation. This result is consistent with recent studies comparing acepromazine and dexmedetomidine as premedication followed by propofol induction (Grasso \textit{et al.}, 2015) and buprenorphine with either acepromazine or dexmedetomidine followed by alfaxalone induction (Herbert \textit{et al.}, 2013). Herbert \textit{et al.} (2013) speculated the lack of difference in induction dose observed in
their study was due to a decrease in cardiac output in dogs receiving dexmedetomidine (Bloor et al., 1992) and the infusion of alfaxalone over 60 seconds was not slow enough to titrate the alfaxalone dose to effect. Rocchi et al., (2013) demonstrated an increase in limb-to-lung circulation time in dogs premedicated IM with 10 µg kg\(^{-1}\) dexmedetomidine alone compared to 0.04 mg kg\(^{-1}\) acepromazine and 0.2 mg kg\(^{-1}\) methadone, suggesting a slower blood flow velocity results from dexmedetomidine administration than acepromazine and methadone. It is possible these differences in doses of dexmedetomidine, acepromazine and methadone resulted in different alterations to the limb-to-lung circulation time than those described by Rocchi et al., (2013) and there was less difference between the two combinations. A delay in delivery of the anaesthetic agent to the central nervous system (CNS), and therefore onset of action in the brain, would result in continuation of delivery of the drug with the methodology used in this study. If limb-to-lung circulation time was increased in dexmedetomidine groups, the continued delivery of induction agent may have resulted in a relative overdose in these groups. The lack of difference in induction dose requirements between the two premedication groups could account for the lack of difference in incidence and duration of apnoea in these groups. It is possible that had a different methodology been used, a difference in the incidence or duration of post-induction apnoea between dogs premedicated with acepromazine or dexmedetomidine may have been detected.

There were some limitations in the design of this study which may have influenced the results obtained. Neither the primary anaesthetist nor the anaesthetist recording duration of apnoea were blinded during the study. Steps were taken to standardise the decision-making process for orotracheal intubation with the aim of reducing the potential subjectivity and bias. The lack of blinding for the recording of the incidence and duration of apnoea was considered not to be a significant problem as the data recorded was objective and the duration of apnoea was timed from the onset of cessation of breathing. The same observer was used to minimise
inter-observer variability and all dogs were anaesthetised by the same experienced anaesthetist to reduce variability.

The lack of significant difference between the two induction drugs with regards to incidence and duration of apnoea, and also the induction dose requirements between premedication groups may be due to a Type II statistical error. A prospective power analysis was performed based on the primary objective of assessing post-induction apnoea and indicated the number of dogs in each group would have adequate power (power = 0.8), however, this does not exclude the possibility of a type II error occurring, particularly given the small group size in this study. The mean duration of apnoea was not statistically different between groups however, the mean duration was between 20 and 30 seconds longer in Groups MD+A and MD+P compared to Groups MA+A and MA+P. This would potentially be a clinically significant difference and the lack of statistical significance in this result may indicate the group size was too small. A larger group size may be able to determine if this difference is significant. Arterial blood gas data could also define specific changes in respiratory function caused by acepromazine or dexmedetomidine, and by propofol or alfaxalone and would have been beneficial in this study.

In conclusion, both alfaxalone and propofol IV caused post-induction apnoea in this population of healthy dogs and the incidence and duration of apnoea was not influenced by the choice of acepromazine or dexmedetomidine premedication IM. Clinicians should be prudent when using IV alfaxalone and propofol following IM premedication with methadone and either acepromazine or dexmedetomidine and should be prepared to provide ventilatory support should post-induction apnoea occur. Further research is required to determine if other factors influence the occurrence of post-induction apnoea following propofol or alfaxalone induction in the dog.
Chapter 4: Effect of rate of administration of propofol or alfaxalone on induction dose requirements and occurrence of apnoea in dogs

4.1 Introduction

Most anaesthetic agents can cause varying degrees of respiratory depression including apnoea. Induction of general anaesthesia frequently causes a period of apnoea commonly referred to as post-induction apnoea which appears to be unrelated to the depth of anaesthesia (Haskins, 2015). Apnoea is considered a serious adverse event of anaesthesia as it can result in hypoxemia, respiratory acidosis and ultimately death if left untreated. In addition, post-induction apnoea can compromise the transition from intravenous (IV) induction to anaesthetic maintenance by a volatile agent due to reduced uptake of inspired gases (Spens and Drummond, 1996; Keates and Whittem, 2012).

Propofol (a phenol compound) and alfaxalone (a neuroactive steroid) are IV anaesthetic agents that interact with the gamma aminobutyric acid (GABA)A receptor to enhance the inhibitory action of endogenous GABA and are commonly used in small animal anaesthesia (Amengual et al., 2013). Propofol and alfaxalone are characterized by rapid and smooth induction of general anaesthesia (Maney et al., 2013), although both drugs exhibit dose-dependent cardiorespiratory depressive properties (Muir and Gadawski, 1998; Muir et al., 2008). Post-induction apnoea following administration of propofol has been well-documented in both human (Taylor et al., 1986; Stokes and Hutton, 1991) and animal studies (Muir and Gadawski, 1998; Muir et al., 2009; Amengual et al., 2013), however, there are contradictory reports regarding the incidence of post-induction apnoea following alfaxalone administration in dogs and cats (Ambros et al., 2008; Muir et al., 2008; Martinez Taboada and Murison, 2010; Keates and Whittem, 2012; Maney et al., 2013).
Most IV anaesthetic agents display a time lag between their plasma drug concentration and sufficient effect site drug concentration to cause induction of anaesthesia (Flood and Shafer, 2015). This hysteresis, or effect site equilibration time, depends on a number of factors including the physicochemical properties of the drug, cardiac output, first-pass pulmonary uptake, the dose administered, and the rate of administration of the drug (Stokes and Hutton, 1991; Berthoud et al., 1993; Dugdale et al., 2005). A reduction in the dose required for induction of general anaesthesia with propofol, eltanolone, etomidate, and thiopentone has been demonstrated in humans using rates of administration slower than originally recommended (Stokes and Hutton, 1991; Berthoud et al., 1993; Myint et al., 1994). The dose reduction at slower rates of administration has also been documented when using propofol in sheep (Ludbrook and Upton, 1997), thiopentone in dogs (Dugdale et al., 2005), and alfaxalone in cats (Bauquier et al., 2015). The effect of altering the rate of administration of propofol or alfaxalone on the induction dose required to induce general anaesthesia and the incidence of post-induction apnoea in dogs has not been reported. The aim of this study was to evaluate the influence of the rate of administration of propofol or alfaxalone for induction of general anaesthesia following premedication with dexmedetomidine and methadone in healthy dogs. Our first hypothesis was that the total dose of either propofol or alfaxalone required to allow orotracheal intubation would be reduced when they were given at a slower rate of administration. The second hypothesis was that the incidence and duration of post-induction apnoea associated with either drug would be reduced when they were delivered at a slower rate of administration than the current guidelines of alfaxalone at a rate of 2 mg kg⁻¹ minute⁻¹ (Jurox Pty Ltd, 2011), or propofol at a rate of 4 mg kg⁻¹ minute⁻¹ (Abbott Laboratories, 2015).
4.2 Materials and methods

4.2.1 Animals

This study was approved by the University of Melbourne Animal Ethics Committee (Ethics ID: 1513466.1) and informed written owner consent was obtained prior to enrolment.

A prospective sample size calculation (IBM SPSS Sample Power 3, SPSS Inc., IL, USA) indicated 15 dogs would be required to represent each rate of administration (Fast and Slow) to provide sufficient power to detect a 15% difference in the incidence or mean duration of apnoea with a study power of 80% and alpha value of 0.05. A difference of 15% was arbitrarily selected as it was believed to represent a reasonable choice providing adequate clinical difference (10 seconds for each minute of apnoea with a standard deviation of 0.45 seconds) without excessively compromising on specificity. Therefore, thirty-two client-owned dogs scheduled to undergo ovariohysterectomy, ovariectomy or castration were recruited into the study.

Exclusion criteria included cardiorespiratory abnormalities detected on physical examination, abnormal packed cell volume or total solids, American Society of Anesthesiologists (ASA) status greater than I, brachycephalic conformation, or patients receiving medications with known sedative effects such as phenobarbital, benzodiazepines, gabapentin, tramadol or other opioids.

4.2.2 Study Protocol

All dogs were admitted to hospital on the morning of the study. Owners were instructed to withhold food for at least eight hours but to allow access to water ad libitum on the night before admission. Dogs were randomly allocated to one of four protocol groups (A-Slow, A-Fast, P-Slow, or P-Fast) using computer generated random numbers (Microsoft Excel 2010; Microsoft Corp. WA, USA). The rate of administration of alfaxalone (Alfaxan, Jurox,
Australia) in the A-Slow group was 0.5 mg kg⁻¹ minute⁻¹ and in group A-Fast the rate was 2 mg kg⁻¹ minute⁻¹. The rate of administration of propofol (Provive 1%, Claris Lifesciences, NSW, Australia) in group P-Slow was 1 mg kg⁻¹ minute⁻¹ and in group P-Fast the rate was 4 mg kg⁻¹ minute⁻¹. An initial physical examination was performed and respiratory rate (f_R), heart rate (HR), and temperature were recorded. Oscillometric arterial blood pressure [systolic (SAP), diastolic (DAP) and mean (MAP)] was monitored using a PetMAP device (PetMAP Graphic, Ramsey Medical, Inc., FL, USA) as part of best practice standards however, the values are not reported for the purpose of this study. Panting was standardized to 100 breaths minute⁻¹ for the purpose of statistical analysis. All dogs were premedicated intramuscularly (IM) in the cervical muscles with 0.5 mg kg⁻¹ methadone (Methone, Ceva Animal Health, Glenorie, NSW, Australia) and 5 µg kg⁻¹ dexmedetomidine (Dexdomitor, Zoetis, NSW, Australia). Approximately 15 minutes after premedication a 20 gauge or 22 gauge catheter was placed in a cephalic vein. Thirty minutes after premedication the post-premedication f_R, HR, SAP, MAP, DAP and temperature was recorded. The degree of sedation was assessed and scored by the same trained observer (SEB) using a previously published scale (Hofmeister, Chandler and Read, 2010) (Appendix S1).

At the completion of the assessment of sedation all dogs were then preoxygenated for 5 minutes via a face mask attached to an appropriately sized circle rebreathing system with oxygen (O₂) delivered at 4 L minute⁻¹. Baseline oxygen saturation of haemoglobin (SpO₂) and HR were measured continuously during the preoxygenation phase using a multiparametric monitor (SurgiVet CDS 2000, Smiths Medical PM Inc. WI, USA) with the probe placed on the upper lip or tongue of the dog. Respiratory rate was also measured via observation of chest excursions prior to induction. Induction of anaesthesia and orotracheal intubation were conducted by the same experienced anaesthetist (SEB) in all cases. Anaesthesia was induced in all dogs by delivering the protocol agent IV via the cephalic
catheter at the previously described rate of administration with a syringe driver using an appropriately sized device-compatible syringe (Baxter Flo-Gard GSP Syringe Pump, Baxter Healthcare Pty Ltd Australia) until orotracheal intubation could be achieved. In order to minimize bias on the part of the ‘non-blinded’ anaesthetist performing the orotracheal intubation, a standardized methodology was followed. The anaesthetist observed that the dog was unable to support its head at which time they assessed the jaw tone. If the jaw tone was minimal to absent and no resistance was met when gentle traction was applied to the tongue, orotracheal intubation was attempted. If the jaw tone was sufficient to prevent intubation, the anaesthetist allowed 10 seconds to elapse before testing the jaw tone again. If the animal coughed or resistance to passing the endotracheal tube (ETT) was met, the process was halted for 10 seconds before attempting intubation again. Immediately upon successful orotracheal intubation, the induction agent infusion was stopped and the ETT was connected to the rebreathing system. The ETT cuff was inflated using pressure change in the pilot balloon as a guide. Delivery of isoflurane (Isoflo, Abbott, Australia) was initiated with a vaporizer setting of 2% in O₂ at a flow rate of 2 L minute⁻¹. A positive pressure breath-hold leak test of the ETT cuff was performed after ventilation resumed.

An additional anaesthetist (JEC) monitored respiration from the time of starting the infusion of induction agent and recorded the occurrence and duration of post-induction apnoea. Apnoea was defined as cessation of breathing for a period of 30 seconds or greater. The HR and SpO₂ were monitored throughout induction of anaesthesia and the apnoeic period using the same monitor and probe position as previously described. The period of apnoea ended when spontaneous breathing returned. If SpO₂ decreased below 90% the anaesthetist intervened and started manual ventilation (MV) by administering a positive pressure breath to 12-15 cm H₂O using the rebreathing bag every 15 seconds until SpO₂ increased to at least 95% and spontaneous ventilation had resumed.
Post-induction measurements of SpO2, end tidal partial pressure of carbon dioxide ($P_{E}^{'\text{CO}_2}$), SAP, DAP and MAP, and lead II ECG were recorded three minutes after completion of orotracheal intubation, or upon initiation of MV if the SpO2 decreased below 90%. If apnoea occurred, HR and SpO2 were monitored and recorded throughout the apnoeic period however; the remaining monitoring devices were not attached to the dog until after the first spontaneous breath in order to prevent any unnecessary stimuli that might influence respiratory drive. From the post-induction measurements onwards HR, $f_r$, SpO2, $P_{E}^{'\text{CO}_2}$, SAP, DAP, and MAP were monitored and recorded every five minutes. Body temperature was monitored via an oesophageal temperature probe and recorded every 15 minutes during the surgical procedure. In addition, all dogs received lactated Ringer’s solution (Compound sodium lactate, Fresenius Kabi, Australia) IV at a rate of 10 mL kg⁻¹ hr⁻¹ for the duration of anaesthesia. Hypotension, defined as MAP less than 60 mmHg, was treated by decreasing the isoflurane vaporizer setting by 0.5% every 5 minutes, administering 10 mL kg⁻¹ of LRS IV over 10 minutes or by dopamine (Dopamine hydrochloride; Hospira, Australia) infusion IV started at 7 µg kg⁻¹ minute⁻¹ and adjusted based on blood pressure response as deemed appropriate by the anaesthetist until MAP increased above 60 mmHg. Manual ventilation was provided during anaesthesia after the initial induction phase if $P_{E}^{'\text{CO}_2}$ increased above 60 mmHg. All dogs were administered 0.2 mg kg⁻¹ meloxicam (Metacam, Boehringer Ingelheim, Australia) subcutaneously at the end of anaesthesia.

4.2.3 Statistical analysis

Data were tested for normality using the Ryan-Joiner test. Sedation scores were analysed with 2-sample T tests and proportion of dogs panting and incidence of apnoea was analysed by Fisher’s exact test. Duration of apnoea was analysed with one-way ANOVA with Tukey test for post-hoc analysis where significant differences were found. Pearson’s correlation
coefficient was calculated for the variable relationship of induction dose and duration of apnoea. The non-parametric data sets of weight, gender and age were analysed with the Kruskal-Wallis test. Significance was set at $p < 0.05$ for all analyses. Analysis was performed using Minitab 17 Statistical Software (Minitab Inc., PA, USA) and GraphPad Prism 6 for Windows (GraphPad Software Inc., CA, USA). Results are presented as mean ± SD or median (range) as appropriate.

**4.3 Results**

Thirty-two dogs of various breeds were enrolled and all dogs completed the study. The dogs were of various breeds, between 5 months and 54 months of age, weighing between 2.0 and 48.2 kg. The groups were not different in terms of age ($p = 0.484$), sex ($p = 0.189$), or body weight ($p = 0.364$). There was no difference in sedation scores between the groups ($p = 0.336$) and all dogs were adequately sedated for catheter placement (Table 3). The induction dose for the A-Slow group was $0.9 ± 0.3$ mg kg$^{-1}$; A-Fast group was $2.2 ± 0.5$ mg kg$^{-1}$, P-Slow group was $1.8 ± 0.6$ mg kg$^{-1}$, and P-Fast group was $4.1 ± 0.7$ mg kg$^{-1}$ (Table 3). There was a difference in dose in mg kg$^{-1}$ between the A-Slow and A-Fast groups ($p \leq 0.001$), and between the P-Slow and P-Fast groups ($p \leq 0.001$). No dogs exhibited excitement or myoclonus during induction.
**Table 2** Sedation score, induction doses of intravenous alfaxalone (A) or propofol (P) and the duration and incidence of apnoea in dogs following intramuscular premedication with methadone 0.5 mg kg\(^{-1}\) and dexmedetomidine 5 µg kg\(^{-1}\) and intravenous induction of anaesthesia with A or P at different rates of administration.

<table>
<thead>
<tr>
<th>Group</th>
<th>Sedation Score</th>
<th>Induction Dose (mg kg(^{-1}))</th>
<th>Duration of Apnoea (seconds)</th>
<th>Incidence of Apnoea (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-Slow</td>
<td>13 ± 2</td>
<td>0.9 ± 0.3*</td>
<td>43 ± 80‡</td>
<td>25</td>
</tr>
<tr>
<td>A-Fast</td>
<td>12 ± 3</td>
<td>2.2 ± 0.5</td>
<td>287 ± 125</td>
<td>100</td>
</tr>
<tr>
<td>P-Slow</td>
<td>11 ± 2</td>
<td>1.8 ± 0.6†</td>
<td>10 ± 18§</td>
<td>25</td>
</tr>
<tr>
<td>P-Fast</td>
<td>13 ± 2</td>
<td>4.1 ± 0.7</td>
<td>247 ± 125</td>
<td>100</td>
</tr>
</tbody>
</table>

Data are means ± standard deviation. Groups: A-Slow, alfaxalone 0.5 mg kg\(^{-1}\) min\(^{-1}\); P-Slow, propofol 1 mg kg\(^{-1}\) min\(^{-1}\); A-Fast, alfaxalone 2 mg kg\(^{-1}\) min\(^{-1}\); and P-Fast, propofol 4 mg kg\(^{-1}\) min\(^{-1}\). Sedation score: range -10 (no sedation) to 14 (profound sedation). *Different from A-Fast (\(p = 0.007\)), †different from P-Fast (\(p = 0.007\)), ‡different from A-Fast (\(p ≤ 0.000\)), §different from P-Fast (\(p ≤ 0.000\)).
Analysis of the incidence of apnoea in each group revealed there were no differences between the two Slow groups (incidence of 25% for both drugs), or between the two Fast groups (incidence of 100% in both groups). The mean duration of apnoea was also not different between the two Slow groups ($p = 0.986$), or between the two Fast groups ($p = 0.962$). There was a difference in duration of apnoea between the Slow and Fast groups of each drug. The duration of apnoea for the A-Slow group (43 ± 80 seconds) was shorter compared to A-Fast (287 ± 125 seconds) ($p \leq 0.001$). The duration of apnoea in the P-Slow group (10 ± 18 seconds) was also shorter compared P-Fast group (247 ± 125 seconds) ($p \leq 0.001$). There was also a strong positive correlation between induction drug dose and duration of apnoea for both alfaxalone ($r = 0.766$, $p = 0.001$) and propofol ($r = 0.825$, $p \leq 0.001$) (Table 3, Figures 3 & 4).
**Figure 3** Correlation between intravenous Alfaxalone induction dose requirement to induce anaesthesia in healthy dogs (mg kg$^{-1}$) and duration of apnoea (seconds), following intramuscular premedication with methadone 0.5 mg kg$^{-1}$ and dexmedetomidine 5 µg kg$^{-1}$. R = 0.766, p = 0.001.
Figure 4 Correlation between intravenous propofol induction dose requirement to induce anaesthesia in healthy dogs (mg kg$^{-1}$) and duration of apnoea (seconds) following intramuscular premedication with methadone 0.5 mg kg$^{-1}$ and dexmedetomidine 5 µg kg$^{-1}$. 

R= 0.825, p ≤ 0.001.
Respiratory rates are shown in Table 4. Panting was a common feature in many dogs in all groups prior to premedication. A significant number of patients in A-Fast and P-Fast groups were still apnoeic at the first measurement (3 minutes after induction) resulting in many missing data points; therefore Pe´CO₂ was analysed from the second measurement (8 minutes after completion of intubation) onward. P-Slow had significantly lower Pe´CO₂ than P-Fast at the second measurement (p = 0.024) but was not statistically significantly different from A-Slow and A-Fast. The Pe´CO₂ was not statistically significantly different between groups at any other times in the study period. There were no statistically significant differences in SpO₂ between groups either after premedication or at any time during the study. One dog in the P-Fast group desaturated after 175 seconds of apnoea. Manual ventilation was initiated immediately and SpO₂ increased to 95% within 60 seconds.
Table 3 Respiratory rate ($f_R$) in breaths minute$^{-1}$ in dogs before premedication (Initial $f_R$), following intramuscular premedication with methadone 0.5 mg kg$^{-1}$ and dexmedetomidine 5 µg kg$^{-1}$ (Post-premedication $f_R$), and 3 minutes after intravenous induction of anaesthesia with alfaxalone (A) or propofol (P) at different rates of administration (Post-induction $f_R$).

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial $f_R$ (range)</th>
<th>Post-premedication $f_R$ (range)</th>
<th>Post-induction $f_R$ (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-Slow</td>
<td>46 (24-100)</td>
<td>22 (16-28)</td>
<td>8 (0-20)*</td>
</tr>
<tr>
<td>A-Fast</td>
<td>64 (20-100)</td>
<td>51 (12-100)</td>
<td>1 (0-5)*†</td>
</tr>
<tr>
<td>P-Slow</td>
<td>49 (20-100)</td>
<td>36 (12-100)</td>
<td>9 (0-16)*†</td>
</tr>
<tr>
<td>P-Fast</td>
<td>66 (16-100)</td>
<td>26 (12-80)*</td>
<td>0 (0)*†</td>
</tr>
</tbody>
</table>

Data are median (range). Groups: A-Slow, alfaxalone 0.5 mg kg$^{-1}$ min$^{-1}$; P-Slow, propofol 1 mg kg$^{-1}$ min$^{-1}$; A-Fast, alfaxalone 2 mg kg$^{-1}$ min$^{-1}$; and P-Fast, propofol 4 mg kg$^{-1}$ min$^{-1}$. * $f_R$ different from initial $f_R$ ($p < 0.005$), † $f_R$ different from post-premedication $f_R$ ($p < 0.05$).

4.4 Discussion

The aim of this study was to evaluate the influence of the rate of administration of two IV induction agents on the induction dose requirement of each drug and the incidence and duration of post-induction apnoea in healthy dogs. The results of this study indicate that the rate of administration affects the amount of both propofol and alfaxalone required to induce general anaesthesia in healthy dogs. The induction dose required to facilitate intubation for both drugs was significantly lower in the A-Slow and P-Slow administration rate groups compared to the A-Fast and P-Fast administration groups.

The induction dose of propofol required in the P-Fast group was similar to the dose reported by Kojima et al., (2002) and Sano et al., (2003b) following premedication with acepromazine or midazolam and butorphanol, but higher than that reported by Grint et al.,
(2010) in dogs premedicated with either acepromazine or medetomidine and buprenorphine. The rate of administration in all studies was slightly different. However, Grint et al., (2010) used a different rate of administration of propofol for each premedication combination examined, the induction dose of propofol in the P-Slow group is similar to the induction dose of the slowest rate of administration reported in that study.

There was also a significant reduction in alfaxalone required for induction in the A-Slow group in this study. The A-Slow group mean induction dose was similar to the dose and rate of administration reported by Maddern et al. (2010) in dogs premedicated with medetomidine and butorphanol. Quirós Carmona et al. (2014) reported an alfaxalone induction dose of 2.04 mg kg⁻¹ in dogs premedicated with dexmedetomidine when alfaxalone was given over 60 seconds. This dose and rate of administration was close to the dose required and rate used in the A-Fast group in this study. These results confirm our hypothesis that the induction dose required to achieve general anaesthesia of both alfaxalone and propofol are increased when these drugs are administered at faster rates.

Previous studies in humans and other species indicate propofol biophase kinetics has a slow equilibrium phase between the blood and the brain and appears to have a finite transport time to reach effective concentrations in the brain (Stokes and Hutton, 1991; Larsson and Wahlström, 1994). Slower rates of administration allow the concentration of propofol to increase in the brain with a lower total dose than fast administration (Stokes and Hutton, 1991; Ludbrook et al., 1998). The slow propofol blood-brain transfer rate, in conjunction with faster infusion rates, creates an accumulation of propofol concentration in the blood which eventually causes a higher peak concentration of propofol in the brain, potentially increasing unwanted side effects such as post-induction apnoea (Stokes and Hutton, 1991). Physiological modelling of propofol in sheep has demonstrated that the amount of propofol in the brain required to induce anaesthesia is the same, regardless of the
rate of administration of the drug and also showed that rapid administration increases the arterial concentration of propofol, but does not result in faster transfer of propofol in to the central nervous system (CNS) (Ludbrook and Upton, 1997). The results of this study support the theory that there is a limit to the rate of uptake of propofol in to the CNS and administering drugs faster than this rate of equilibration can potentially result in relative overdosing. Administering IV anaesthetic agents at a slower rate allows for a sustained gradient between plasma and CNS to develop which can reduce the likelihood of administering a relative overdose of induction agent.

As with propofol, in the current study we observed a reduction in the alfaxalone induction dose requirement with a slower infusion rate. A recent study in cats found a similar reduction in induction dose requirements when alfaxalone was administered at a quarter of the rate recommended by the manufacturer (Bauquier et al., 2015). Although no data regarding the biophase kinetics of alfaxalone exists, a slow equilibrium phase between the blood and brain is a possible explanation for the reduction in dose requirement observed.

The results of this study indicate the rate of administration of both propofol and alfaxalone does influence the incidence and duration of post-induction apnoea and this is most likely related to the total dose required to achieve general anaesthesia at the different rates of administration. The incidence and duration of post-induction apnoea was lowest in the A-Slow and P-Slow groups, both groups having an incidence of 25% apnoea. These groups required significantly lower doses of induction agent to achieve general anaesthesia than the A-Fast and P-Fast groups. Results from previous studies in unpremedicated dogs indicate that increasing doses of propofol and alfaxalone cause increased incidence and duration of apnoea (Muir and Gadawski, 1998; Muir et al., 2008; Keates and Whittem, 2012).

Respiratory depression during anaesthesia is due to depression of inspiratory drive in the cortex and brainstem, decreased ventilatory response to increasing arterial CO₂, decreased
excitatory glutamate neurotransmitters and increased GABA concentration (Goodman et al., 1987; Lambert et al., 2003). These effects are dependent on the dose of hypnotic anaesthetic agent concentration in the brain, and as the concentration in the brain increases, so do the depressant effects on respiration. As the rate of administration of IV anaesthetic agents does not influence the rate of equilibration between plasma and the brain, administering these drugs faster causes them to accumulate in the plasma before being transferred to the CNS where the increased concentration beyond that necessary to cause anaesthesia (i.e. an overdose) leads to increased depression of the CNS and unwanted negative effects such as apnoea.

The incidence of apnoea in the A-Fast and P-Fast groups in this study were higher than those reported by Muir and Gadawski (1998) for propofol, Muir et al. (2008) for alfaxalone, and Amengual et al. (2013) and Okushima et al., (2015) for both propofol and alfaxalone. While the rate of administration clearly affects the incidence and duration of post-induction apnoea, the influence of premedication drugs should also be considered. Dexmedetomidine (an alpha-2 adrenergic agonist) and methadone (a synthetic pure µ opioid receptor agonist) were administered IM to all dogs in this study and cause dose-dependent respiratory depression with a synergistic effect when administered together (Rankin, 2015). Apnoea is a reported complication following propofol and alfaxalone administration in dogs premedicated with fentanyl alone (Okushima et al., 2015) or acepromazine and pethidine (Amengual et al., 2013). Amengual et al. (2013) reported 11/30 dogs receiving 3 mg kg⁻¹ propofol and 7/29 dogs receiving 1.5 mg kg⁻¹ alfaxalone following acepromazine and pethidine premedication were still apnoeic 5 minutes (the end point of the study) after administration of the induction agent over 5 seconds however, a higher incidence of post-induction apnoea was observed in this study (100% in A-Fast and P-Fast groups). In the study by Amengual et al. (2013) a set dose was administered which was lower than the mean
induction dose of propofol and alfaxalone in the Fast groups in this study. This difference in induction dose is the most likely reason a higher incidence of apnoea was observed in the current study. The reduction in incidence and duration of apnoea in the A-Slow and P-Slow groups suggests the rate of administration influences total induction dose and therefore incidence and duration of apnoea more than the effect of the chosen premedication drugs. Further investigation using different combinations of premedication drugs are warranted to confirm this effect.

There were no statistical or clinically significant differences in SpO2 between groups either after premedication or at any time during the study. All dogs in the study were preoxygenated for 5 minutes prior to induction in an effort to prevent clinically significant decreases in SpO2. McNally et al., (2009) reported preoxygenation for 3 minutes increased the time to desaturation (approximately 300 versus 70 seconds) compared to dogs breathing room air when sedated with acepromazine and morphine and induced with propofol. The SpO2 of one dog in the P-Fast group dropped below 90% after 175 seconds of apnoea however this dog responded well to MV. Apnoea causes reduced alveolar ventilation, most likely leading to the decrease in SpO2 observed in this dog as there was an almost immediate increase in SpO2 in response to MV. Other possible causes could have been peripheral vasoconstriction due to dexmedetomidine or compression of the vessels in the tongue by the probe resulting in poor blood flow and therefore an erroneous SpO2 reading, or equipment malfunction such as electrical or ambient light interference causing an error in the probe reading.

There were some limitations in the design of this study which may have influenced the results. The primary anaesthetist and the anaesthetist recording duration of apnoea were aware of treatment allocation. Steps were taken to standardize the decision-making process for orotracheal intubation with the aim of reducing the potential subjectivity and bias. The
lack of ‘blinding’ for the recording of the incidence and duration of apnoea was considered not to be a significant problem as the data recorded was objective and the duration of apnoea was timed from the onset of cessation of breathing. The same observer was used to minimize inter-observer variability and all dogs were anesthetized by the same experienced anaesthetist to reduce variability. Monitoring of respiration and oxygenation was through non-invasive techniques and invasive arterial blood gas analysis was not performed in this study. The use of P\textsubscript{E}CO\textsubscript{2} as a parameter is limited when patients are not exhaling and, as MV was not provided unless the patient’s oxygen saturation decreased below a pre-set level, it was not possible to monitor increases in P\textsubscript{E}CO\textsubscript{2} in response to the induction agents used. While assessment of PaCO\textsubscript{2} and PaO\textsubscript{2} were not part of the primary objective, they may have added information that could assist in explaining the results obtained.

Only two rates of administration of each drug were tested in this study. While differences in induction dose were detected using these rates, it is not possible to conclusively state the ideal rate of administration of either propofol or alfaxalone based on these results. Apnoea was still a feature in 25% of dogs in both the A-Slow and P-Slow groups. Further research is required to identify optimal rates of administration of these drugs to minimize adverse effects such as post-induction apnoea. Finally, the lack of significant difference between the two induction drugs may be due to a Type II statistical error. A prospective power analysis was performed and indicated the number of dogs in each group would have adequate power (power = 0.8), however this does not exclude the possibility of a type II error occurring, particularly given the small group size in this study.

In conclusion, both alfaxalone and propofol caused post-induction apnoea in this population of healthy dogs and the incidence and duration of apnoea was reduced when the rate of administration of both induction drugs was decreased. Current manufacturer recommended administration protocols of both alfaxalone and propofol resulted in an
increased requirement in induction dose to induce anaesthesia, which can result in increased incidence of post-induction apnoea. Further research is required to determine the plasma-CNS biophase kinetics of alfaxalone and to determine the ideal rate of administration of propofol and alfaxalone for induction of anaesthesia to minimize adverse effects of these agents. Unless contraindicated, the authors recommend reducing the total dose and the rate of administration of both propofol and alfaxalone in clinical settings.
Chapter 5: Conclusions

Post-induction apnoea is a common sequela to the administration of intravenous anaesthetic agents in many species. The mechanisms by which anaesthetic drugs cause depression of the respiratory centres of the brain remain largely unknown. This thesis has attempted to identify the effect on respiratory function of two sedative agents commonly used in dogs (acepromazine and dexmedetomidine) immediately after induction of anaesthesia with either propofol or alfaxalone. Evidence from previous studies indicated both propofol and alfaxalone could cause post-induction apnoea in dogs. The differences in experimental protocols used, study populations (laboratory-bred dogs or clinical patients), and even how long without spontaneous breathing constituted post-induction apnoea makes it difficult to compare the previous studies or identify trends in results between propofol and alfaxalone. The information previously available did not clearly identify if there was a difference in the incidence or duration of post-induction apnoea between propofol and alfaxalone when used in dogs. The effect of differences in doses used and methods of administration of these drugs on post-induction apnoea were not entirely clear.

The methods used in this study and the study population reflect those of a typical general veterinary practice. Clinically relevant doses of both premedication sedative agents (acepromazine and dexmedetomidine) and anaesthetic induction agents (propofol and alfaxalone) were tested in a typical population of healthy dogs presented to a veterinary hospital for routine surgery. This study did not identify any difference in the incidence or duration of post-induction apnoea in dogs following premedication with either acepromazine or dexmedetomidine and induction with alfaxalone or propofol. Due to the limitations of the study population it was not possible to measure invasive pulmonary variables such as PaO₂.
and PaCO₂. The ability to measure these particular variables may elucidate differences in the respiratory effects of these two drugs. In addition, larger sample sizes may be better able to detect statistically significant differences between these drug combinations. The clinical relevance of any difference however, appears negligible.

What did become apparent during the collection of data in these studies, is the effect of the rate of administration on both the dose of alfaxalone or propofol required to induce anaesthesia, and the incidence and duration of post-induction apnoea. When alfaxalone or propofol is administered at a slow rate, the amount of drug required to induce anaesthesia sufficient to allow orotracheal intubation is much lower than when either of these drugs are administered quickly. The induction drugs in these studies were administered with a syringe driver, which allows for accurate timing and dosing however, this is not a standard method of administering these drugs. One limitation of these studies is the practicality of applying such a slow rate of administration when administering these drugs by hand injection. While it may not be possible to administer intravenous induction agents as specifically as the methods in these studies, a sensible recommendation for practitioners in general practice would be to administer these drugs as slowly as practically possible to reduce the risk of adverse ventilatory effects.

Apnoea during anaesthesia is still a common event with potentially negative effects. Any veterinarian performing anaesthesia in dogs must be aware of the potential for this to occur and they should be comfortable in their ability to monitor for, and detect, any apnoeic event. This study indicates the potential for post-induction apnoea to occur with the two most commonly utilised induction agents in small animal anaesthesia is very similar, regardless of premedication sedative used. There are numerous other combinations of drugs used for premedication in dogs, and the effect of these on post-induction apnoea is an area for further research. Identifying a more specific ideal rate of administration of alfaxalone or propofol in
dogs that maximises speed of onset of anaesthesia while minimising adverse events is also an avenue for further development. As we move towards implementation of international treaties that will prohibit emissions of chlorofluorocarbons found in the current commercially available inhalant agents by 2030, it will become more important to fully understand the effects and interactions of the sedatives and intravenous anaesthetic agents available in order to be able to provide safe anaesthetic events to all species.
References


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Appendix S1. Sedation score system used 30 minutes after premedication.

<table>
<thead>
<tr>
<th>Observation</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vocalisation</td>
<td>0</td>
<td>Quiet</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>Whining softly but quiets with soothing touch</td>
</tr>
<tr>
<td></td>
<td>-2</td>
<td>Whining continuously</td>
</tr>
<tr>
<td></td>
<td>-3</td>
<td>Barking continuously</td>
</tr>
<tr>
<td>Posture</td>
<td>3</td>
<td>Lateral recumbency</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Sternal recumbency</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Sitting or ataxic while standing</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Standing</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>Moving continuously</td>
</tr>
<tr>
<td>Appearance</td>
<td>3</td>
<td>Eyes sunken, glazed or unfocused; ventromedial rotation</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Eyes glazed but follow movement</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Protrusion of nictitating membrane, normal visual responses</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Normal appearance</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>Pupils dilated; abnormal facial expression</td>
</tr>
<tr>
<td>Interactive behaviour</td>
<td>3</td>
<td>Recumbent; no response to voice or touch</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Recumbent; lifts head in response to voice or touch</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Recumbent but stands in response to voice or touch</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Standing or sitting up; normal response to voice or touch</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>Moves away from voice or touch; appears anxious</td>
</tr>
<tr>
<td></td>
<td>-2</td>
<td>Growls or hisses when approached or touched</td>
</tr>
<tr>
<td></td>
<td>-3</td>
<td>Bites or swats when approached</td>
</tr>
<tr>
<td>Restraint</td>
<td>2</td>
<td>Lies on floor with minimal restraint needed</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Lies on floor with light restraint of head or neck</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Sits up on floor; attempts to jump despite restraint</td>
</tr>
<tr>
<td></td>
<td>-1</td>
<td>Struggles continuously against restraint</td>
</tr>
<tr>
<td></td>
<td>-2</td>
<td>Cannot be restrained for &gt; 20 seconds</td>
</tr>
<tr>
<td>Response to noise</td>
<td>3</td>
<td>No response to a hand clap near the head</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Minimal response to a hand clap near the head</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Slow or moderate response to a hand clap near the head</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Brisk response to a hand clap near the head; raises head with eyes open</td>
</tr>
</tbody>
</table>
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