A CLINICAL STUDY OF INHALANT ANAESTHESIA IN DOGS

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Apart from the assistance which is acknowledged herein,
this thesis represents the original work of the author.

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Summary

A clinical trial was undertaken using three different inhalant anaesthetic agents and one intravenous anaesthetic agent in dogs undergoing routine desexing surgery.

Healthy adult dogs undergoing either ovariohysterectomy or castration were assessed as to their demeanour, with the more excitable dogs being placed in groups receiving premedication with acepromazine and morphine. All dogs were then randomly assigned an anaesthetic agent for induction of general anaesthesia. The agents were the inhalants halothane, isoflurane and sevoflurane, and the intravenous agent propofol. Inhalant inductions were undertaken using a tight fitting mask attached to a standard anaesthetic machine with a rebreathing circuit, with the maximum dose of inhalant available from a standard vaporiser. Propofol inductions were undertaken via intravenous catheter. Dogs induced with propofol were randomly assigned one of the three inhalant agents for maintenance. Those induced by inhalant agent were maintained using the same agent. The surgical procedure was undertaken in standard fashion, as was recovery from anaesthesia. All dogs received the non-steroidal anti-inflammatory agent meloxicam.

Data collection was divided into three stages: induction, maintenance, and recovery from anaesthesia. Variables measured at induction of anaesthesia were time to intubation, number of intubation attempts, tolerance of mask, quality of induction and quality of transfer to the maintenance stage. Standard variables for monitoring of anaesthesia were recorded throughout the maintenance of anaesthesia. Variables measured at recovery were time to righting, time to standing and quality of recovery.

The mean time to intubation when using the newer inhalant sevoflurane (196.2 ± 14.8sec, mean ± SE) was not significantly different to that for halothane (221.4 ± 14.0sec) or isoflurane (172.4 ± 15.0sec). Time to intubation with isoflurane was significantly faster than with halothane. Mean time to intubation with propofol (85.4 ± 7.7sec) was significantly faster than that for any of the three inhalants. Choice of inhalant had no effect on quality of induction. The use of premedication significantly improved the quality of induction. The use of propofol for induction likewise significantly improved the quality of induction.

Standard cardiorespiratory variables measured during the maintenance phase of anaesthesia remained within normal clinical ranges for all three inhalants, and were therefore not further analysed.

Choice of inhalant agent had no significant effect on the time to righting or standing in recovery. The use of propofol for induction had no effect on these variables. Animals placed in groups receiving premedication had significantly longer times to righting and standing. The oesophageal temperature at the end of the procedure had a significant effect on times to righting and standing, with lower temperatures contributing to slower recoveries. Independent of procedure time, male dogs had shorter times to righting than female dogs.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACP	Acepromazine
ANOVA	Analysis of variance
A$	Australian dollars
Br	Bromine
BP	Barometric pressure
CBF	Cerebral blood flow
°C	Degrees Celsius
CaEDTA	Calcium ethylene diaminetetraacetic acid
CDC	Canine Desexing Clinic
CI	Confidence interval
Cl	Chlorine
cmH_2O	Centimetres of water
$CMRO_2$	Cerebral metabolic requirement for oxygen
CNS	Central nervous system
CO_2	Carbon dioxide
COX-1	Cyclo-oxygenase isoform 1
COX-2	Cyclo-oxygenase isoform 2
dP/dt	Rate of change of pressure over time
$drops.ml^{-1}$	Drops per millilitre
ED_{95}	Estimated dose (95%)
EDTA	Ethylene diaminetetraacetic acid
ECG	Electrocardiogram
EEG	Electroencephalogram
ETA	End-tidal inhalant anaesthetic concentration
F	Fluorine
G	Gauge
GST	Goods and services tax
GWP	Greenhouse Warming Potential
Hal	Halothane
hr	Hour

ICP	Intracranial pressure
Iso	Isoflurane
$IU.ml^{-1}$	International units per millilitre
IM	Intramuscular
kg	Kilogram
$l.min^{-1}$	Litres per minute
m	Metre
MAC	Minimum alveolar concentration
MAP	Mean arterial pressure
$mg.kg^{-1}$	Milligrams per kilogram
$ml.kg.min^{-1}$	Millilitres per kilogram per minute
$mg.ml^{-1}$	Milligrams per millilitre
min	Minute
mmHg	Millimetres of mercury
$ml.min^{-1}$	Millilitres per minute
$ml.sec^{-1}$	Millilitres per second
$ng.ml^{-1}$	Nanograms per millilitre
NSAID	Non-steroidal anti-inflammatory drug
O_2	Oxygen
ODP	Ozone Depletion Potential
OR	Odds ratio
P_A	Alveolar partial pressure
P_V	Venous partial pressure
Pro	Propofol
Q	Cardiac output
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
sec	Second
Sevo	Sevoflurane
SpO_2	Haemoglobin oxygen saturation
$\mu g.ml^{-1}$	Micrograms per millilitre
λ	Blood:gas solubility

Introduction

Inhalation was the only means of delivery of agents for general anaesthesia for almost one hundred years. Whilst indications for the use of intravenous anaesthetics have developed in more recent years, inhalant agents remain widely used in human and veterinary anaesthesia (Steffey 1996). The value of inhalants lies in their flexibility and predictability; primarily for maintenance of anaesthesia, but also for induction.

The development of halothane in the early 1950's represented a significant progression in inhalant anaesthesia. Its fluorinated alkane structure produced a volatile liquid that was non-flammable, and considerably less toxic to the patient than older agents such as diethyl ether (Steffey 1996; Fee and Thompson 1997). However, its side effect profile, and specifically its ability to occasionally produce a fatal acute hepatitis in the human, encouraged the pursuit of superior agents. Isoflurane and sevoflurane were products of this search. Isoflurane, introduced into commercial use in the 1970's, was significantly less soluble in blood than halothane, and was free of the hepatic side effects. It possessed, unfortunately, a notably more irritating smell than halothane. Sevoflurane, although first synthesised in the 1970's, was not released in the US until 1995. It is even less soluble in blood than isoflurane, and has a less irritating odour (Brown 1995; Sinha *et al.* 1996).

Little is known about the method of action of inhalant anaesthetics. It appears likely that immobility is mediated through the action of the agent on the motor interneurons of the spinal cord (Rampil and King 1996), as removal of the entire cerebrum and brainstem does not reduce the inhalant anaesthetic dose requirement to prevent movement in response to stimulus (Rampil *et al.* 1993). It is suggested that the inability to recall events under anaesthesia may be due to effects of the inhalant on higher centres of the brain (Koblin 1994; Eger *et al.* 2002).

Induction of anaesthesia with inhalant agents is dependent upon the interplay of several factors. Increasing cardiac output, minute respiratory volume or the gradient between the alveolar concentration and arterial concentration will increase the speed of induction. Whilst manipulation of cardiac output may be infeasible at the point of induction of anaesthesia, minute respiratory volume may be influenced by the method of inhalant induction and the smell of the inhalant, and the slope of the

concentration gradient is influenced by the inhalant vaporiser settings and gas flow rates used (Eger 1974). A small number of studies have compared the speed and quality of induction of anaesthesia using the modern inhalant agents in the dog. Equipotent doses of 2.0.MAC of isoflurane and sevoflurane delivered a significantly more rapid time to intubation for sevoflurane than isoflurane (Johnson *et al.* 1998). Doses of 2.5.MAC produced similar results, with sevoflurane significantly faster to intubation than isoflurane, which in turn was significantly faster than halothane (Mutoh *et al.* 1995). However, standard practice in many veterinary practices is to use the maximum dose of the inhalant available from a standard vaporiser, which is in excess of 3.0.MAC, particularly for halothane. A previous study examined induction of anaesthesia using halothane and isoflurane at close to maximum vaporiser output, revealing no significant differences in induction speed (Hellebrekers 1986). Recovery from anaesthesia is reliant on the same factors as induction. Dogs anaesthetised with halothane recovered to standing slower than those anaesthetised with isoflurane in an experimental study (Hellebrekers 1986). A similar study of recovery from anaesthesia using isoflurane or sevoflurane could elucidate no differences between the two agents (Johnson *et al.* 1998).

Whilst the newer inhalants have overcome the acute hepatitis occasionally associated with halothane, all three agents do have effects on several body systems which are not beneficial. There are case reports in the human literature of seizure activity associated with sevoflurane anaesthesia (Adachi *et al.* 1992; Terasako and Ishii 1996; Woodforth *et al.* 1997; Kaisti *et al.* 1999; Iijima *et al.* 2000), although similar problems have not been revealed in the dog (Scheller *et al.* 1990). Halothane anaesthesia causes a greater increase in ICP and CBF than that occurring with the two newer inhalants, which may retain these values within normal limits (Scheller *et al.* 1990; Kuroda *et al.* 1997; Monkhoff *et al.* 2001).

All three inhalants have important effects on the cardiovascular system. Halothane's ability to sensitise the heart to catecholamine-induced arrhythmias was a strong motivation for further development of the fluorinated alkane inhalant anaesthetics (Wallin *et al.* 1975; Steffey 1995). The adrenaline concentrations required to cause cardiac arrhythmias in the dog are far higher with isoflurane and sevoflurane than with halothane. All three agents decrease cardiac output (Steffey and Howland 1978; Bernard *et al.* 1992; Mutoh *et al.* 1997), halothane being somewhat more depressive of CO than isoflurane or sevoflurane. The three inhalants are

significant vasodilators (Malan *et al.* 1995; Holzman *et al.* 1996). Although greater vasodilation with the two newer inhalants leads to slightly lower MAP values than with halothane, statistically significant differences have not been demonstrated in several studies (Bernard *et al.* 1990; Frink *et al.* 1992a; Harkin *et al.* 1994; Malan *et al.* 1995; Mutoh *et al.* 1995).

Of the three agents, isoflurane is the most irritant to the respiratory tract, followed by halothane, with sevoflurane being the most benign (Doi and Ikeda 1993). This may well impact on the relative suitability of the three agents for induction of anaesthesia. All three cause depression of ventilation in the anaesthetised patient, isoflurane and sevoflurane both causing greater depression than halothane (Mutoh *et al.* 1995; Mutoh *et al.* 1997).

The development of sevoflurane was delayed by concerns that fluoride ions, produced by metabolism of the agent, and a polyvinyl ether, arising from interaction of the agent with carbon dioxide absorbents, would be deleterious to renal function in the patient (Brown 1995). Whilst this appeared to be an issue in rats, no strong evidence of kidney dysfunction has been found in humans following sevoflurane anaesthesia (Patel and Goa 1996). None of the three agents produce changes in renal blood flow (Gelman *et al.* 1984; Crawford *et al.* 1992). However, blood flow to the liver is reduced, although this is not thought to be of consequence in the absence of other complicating factors (Steffey 1995).

The objectives of the current study were to investigate the speed and quality of anaesthetic induction and recovery using the three inhalants. This was to be carried out in the clinical domain. Whilst previous research in the human field has thoroughly compared the inhalants in the clinical domain, as summarised by Patel and Goa (1996), the veterinary literature is restricted almost entirely to the experimental situation; clinical veterinary studies have only been of a qualitative or non-comparative nature (Mutoh *et al.* 1995; Johnson *et al.* 1998; Tzannes *et al.* 2000; Haitjema and Cullen 2001).

Inhalant agents are not the most common agents used for induction of anaesthesia in private veterinary practice, with the use of intravenous anaesthetic agents more popular (Nicholson and Watson 2001). Propofol is a relatively new intravenous agent, having been first synthesised in the 1970s (Reves *et al.* 1994). It is attractive due to the generally high quality of the induction associated with its use (Weaver and Raptopoulos 1990; Zoran *et al.* 1993), and its ability to be metabolised

outside of the liver (Veroli *et al.* 1992). Induction is rapid, and recovery from a single induction bolus is adjudged complete within approximately 20min (Watkins *et al.* 1987). A reduction in cardiac output of approximately 20% occurs during induction with propofol (Brussel *et al.* 1989), persisting for less than 5min. A period of apnoea lasting approximately 30sec is often associated with induction (Watkins *et al.* 1987; Morgan and Legge 1989; Zoran *et al.* 1993), although the related rise in arterial CO_2 is mild in biological terms (Robertson *et al.* 1992). Paradoxically, propofol is noted to have both proconvulsant and anticonvulsant properties, with trembling and tonic-clonic type activity often noted at induction (Weaver and Raptopoulos 1990; Robertson *et al.* 1992). No published studies have compared the induction of anaesthesia with propofol to that of inhalant agents in the veterinary clinical situation.

Premedication is commonly used in veterinary practice to decrease the dose of induction agent required, to provide analgesia and to increase the quality of induction and maintenance of anaesthesia (Thurmon *et al.* 1996). Acepromazine and morphine provides a suitable neuroleptanalgesic combination for these purposes (Thurmon *et al.* 1996). For those animals undergoing invasive surgery without the benefit of such premedication, some form of postoperative analgesia is important. This may be provided by perioperative use of a non-steroidal anti-inflammatory drug such as meloxicam.

Chapter 1: Literature Review

1.1 Inhalant anaesthetics

1.1.1 History

The earliest agents used for general anaesthesia – nitrous oxide and diethyl ether – were delivered by inhalation, and inhalant agents retain great popularity. Being administered and eliminated by the respiratory tract allows predictable and rapid adjustment of depth of anaesthesia. The most common inhalants used in clinical veterinary practice today are halothane and isoflurane (Nicholson and Watson 2001). Sevoflurane shows potential for supplanting the use of these two agents.

Halothane is the oldest of these three agents, being first synthesised in the early 1950's (Steffey 1996). The ability to commercially produce fluorinated alkanes (*Section 1.1.2*) such as halothane was in fact a fortuitous byproduct of the Manhattan Project (Fee and Thompson 1997). Halothane represented a quantum progression from previous inhaled agents such as ether and chloroform, in being non-flammable and considerably less toxic. However, unfavourable side effects in clinical use encouraged further development, and isoflurane and sevoflurane were both first synthesised in the late 1960's (Brown 1995). Commercial indifference and questions regarding its metabolism and stability stalled further development of sevoflurane, whilst isoflurane was introduced to human anaesthesia practice in the mid 1970's (Steffey 1995). Isoflurane was registered for veterinary use in Australia in 2001. Eventually resurrected by a Japanese pharmaceutical company in 1988, sevoflurane was licensed for human use in that country in 1990, several years before its introduction elsewhere (Brown 1995). Sevoflurane was registered for veterinary use in the USA in 2001, but is currently not registered for veterinary use in Australia.

1.1.2 Chemical composition

With the exception of nitrous oxide, all the "modern" inhalant anaesthetics are halogenated organic compounds. The addition of the halogens chlorine, bromine or fluorine to simple short chain hydrocarbons creates anaesthetic agents which are more potent, less biologically reactive and less flammable than their non-halogenated

counterparts (Steffey 1995). The addition of an ether linkage, as occurs in the composition of isoflurane and sevoflurane, decreases the cardiac arrhythmogenicity of the agent (*Section 1.1.5.2.2*). The use of fluorine over other halogens produces lower potency but greater stability (Steffey 1996).

Relevant chemical data for halothane, isoflurane and sevoflurane is presented in Table 1.1. All three are liquid at room temperature and pressure, with vapour pressures sufficiently high to produce a vapour concentration able to induce general anaesthesia when inhaled. A small quantity of a preservative, thymol, is added to halothane to prolong its shelf life, as it is less stable than its more fluorinated competitors.

	Halothane	***Isoflurane***	***Sevoflurane***
Boiling point (°C)	*50*	*49*	*59*
Vapour pressure (mmHg, 20°C)	*243*	*240*	*160*
Blood:gas solubility coefficient (37°C)	*2.54*	*1.46*	*0.60*
Oil:gas solubility coefficient (37°C)	*224*	*91*	*47*
Ether linkage	*No*	*Yes*	*Yes*
Preservative	*Yes*	*No*	*No*
Halogen	*Br, Cl, F*	*Cl, F*	*F*
Molecular weight (g)	*197.4*	*184.49*	*200.05*
Liquid specific gravity (g/ml)	*1.86*	*1.49*	*1.52*

Table 1.1: Selected, relevant chemical data for halothane, isoflurane and sevoflurane
Br: Bromine
Cl: Chlorine
F: Fluorine

1.1.3 Method of action

Surprisingly little is known about the methods or sites of action of inhaled anaesthetic agents. This is coupled with a difficulty in even defining the term anaesthesia (Eger *et al.* 2002). Whilst many elements may be said to constitute the state of anaesthesia, it has been hypothesised that the fundamental constituents of

anaesthesia are immobility and amnesia – the surgeon wants an immobile patient, the patient wants not to remember the surgeon's attentions (Eger *et al.* 2002). Other elements such as muscle relaxation and suppression of autonomic reflexes are often but not always associated with this state.

It appears likely that immobility is mediated through action by the volatile agent on the spinal cord, possibly due to effects on motor neurons (Rampil and King 1996). Decerebration, or even transection of the spinal cord from the brain, does not decrease the anaesthetic dose required to prevent movement in response to stimulus (Rampil *et al.* 1993).

Amnesia is more likely the result of effects somewhere in the higher centres, potentially the reticular formation, amygdala, hippocampus, or cerebral cortex (Koblin 1994; Eger *et al.* 2002).

1.1.4 Therapeutic effects

1.1.4.1 Dose requirements

Dose requirements for general anaesthesia by inhalant agents are compared by determination of Minimum Alveolar Concentration (MAC). The MAC is defined as the minimum end-expiration anaesthetic concentration sufficient to suppress conscious response in 50% of patients exposed to a standard noxious stimulus, often clamping of an extremity or a mild electric shock (Eger *et al.* 1965). Calculated halothane, isoflurane and sevoflurane MAC values for dogs are presented in Table 1.2. A dose sufficient to produce immobility in 95% of patients (ED_{95}) has been calculated in humans to be 1.2 to 1.4.MAC. Dose requirements for normal surgery may be expected to be similar (Steffey 1996). The MAC will be varied by the use of concurrent medications such as sedatives and intravenous induction agents. It will also be modified by other circumstances such as body temperature, age, variations in blood pressure and systemic disease. The dose requirement is inversely proportional to the agent's oil:gas solubility (Table 1.1), representing the affinity of that agent for lipids, such as the membranes of neuronal tissue.

	Canine MAC (%)	*References*
Halothane	0.86-0.93	Merkel and Eger 1963
Isoflurane	1.28-1.30	Steffey and Howland 1977; Steffey, Baggot *et al.* 1994
Sevoflurane	2.09-2.35	Mutoh, Nishimura *et al.* 1997; Kazama and Ikeda 1988

Table 1.2: Canine dose requirements for inhalant anaesthetics

1.1.4.2 Factors affecting induction of anaesthesia

Halothane, isoflurane and sevoflurane have been used for the induction of general anaesthesia by mask inhalation. The speed and quality of mask induction is dependent upon factors related to the patient and to the agent.

From the point of view of the agent, the most important factors related to induction of anaesthesia are its blood:gas solubility and irritancy to the respiratory tract. A lower blood:gas solubility implies that less of the agent must be absorbed before concentrations will begin to rise in the target tissues, primarily the central nervous system (Dale and Brown 1987; Steffey 1996). As shown in Table 1.1, sevoflurane is considerably less soluble in blood than isoflurane, which in turn is less soluble than halothane. Sevoflurane's advantage over isoflurane in this area is accentuated by sevoflurane's more "pleasant" odour, which improves pulmonary ventilation during induction and is further discussed below (*Section 1.1.5.3.1*).

The most important patient factors influencing the speed of inhalant agent induction of anaesthesia are cardiac output, alveolar ventilation, and the concentration gradient between pulmonary arterial blood and alveolar gas (Eger 1974). As cardiac output increases, a greater volume of blood will pass through the lungs and thus increase the quantity of inhaled agent absorbed from the alveolar gas, decreasing the time required to saturate the blood volume with the agent. Improving alveolar ventilation, the volume of gas inspired and expired by the animal over a given period,

will obviously increase the quantity of agent available to be absorbed by the pulmonary blood flow. The movement of molecules of the inhalant agent from alveolar gas to pulmonary blood is a passive process, and thus will be most rapid in the presence of a strong concentration gradient between the two. In practical terms, this means the swiftest changes in agent concentrations in the central nervous system will be produced by the use of the highest feasible inhaled concentrations. These factors interplay with those related to the agent. Alveolar ventilation, for instance, will be markedly affected by the animal's acceptance of the mask or other means of agent administration, and by the pungency or irritancy of the agent.

The influence of these factors may be expressed in the following equation (Eger 1994):

$$\text{Uptake} = \lambda \,.\, Q \,.\, (P_A - P_V) / BP$$

λ = Blood:gas solubility of agent
Q = Cardiac Output
P_A = Alveolar partial pressure of agent
P_V = Pulmonary venous partial pressure of agent
BP = Barometric pressure

Two experimental studies have compared induction speed and quality using equipotent doses of inhalant agents in the dog. A comparison of isoflurane to sevoflurane for induction of unpremedicated dogs showed sevoflurane induction to be significantly faster and of better quality, taking a mean of 5.7min to endotracheal intubation, compared to 8.6min for isoflurane (Johnson *et al.* 1998). A maximum dose of 2.0.MAC was used for each agent, achieved in several steps over an initial 45sec. Inhalation of 2.5.MAC of halothane, isoflurane and sevoflurane allowed endotracheal intubation in a mean of 13.12, 4.76 and 3.48min respectively (Mutoh *et al.* 1995). Sevoflurane induction was associated with significantly fewer "movements" during mask inhalation than the other two agents, although this term was not further defined. A study described only in abstract form also demonstrated faster induction of anaesthesia with sevoflurane in comparison to isoflurane when equipotent doses of 2.5.MAC were used in premedicated dogs (Cantalapiedra *et al.* 1999). These results

correlate relatively closely with summaries of data from human studies (Patel and Goa 1996).

Vaporiser settings of 2.5.MAC, being at most 2.3, 3.3 and 5.9% for halothane, isoflurane and sevoflurane respectively, are well below the maximum settings available on a standard precision vaporiser such as a Tec 3 (Cyprane, Keighley, England). The maximum inhalant concentrations available on vaporisers for these agents is 5.0, 5.0, and 8.0% respectively. Therefore, these vaporisers allow for maximum delivered concentrations of at least 5.4, 3.8 and 3.4.MAC for the three agents. Using these higher concentrations for inhalant induction is common practice in human and veterinary anaesthesia (Patel and Goa 1996; Agnor, Sikich *et al.* 1998; Haitjema and Cullen 2001; C.Dart, *pers. comm.*). One experimental study compared halothane and isoflurane for induction of anaesthesia in the dog using a vaporiser setting of 4.5%, achieved by increasing vaporiser setting by 0.5% every 60sec (Hellebrekers 1986). This equates to approximately 4.8.MAC and 3.5.MAC for halothane and isoflurane respectively. Using this protocol, no significant difference was seen between the two agents in terms of time to intubation, which was achieved in 7.1 to 7.5min in both groups.

A small number of studies have investigated the speed of induction of anaesthesia using roughly equipotent doses of isoflurane or sevoflurane in the cat. In clinical patients undergoing desexing, induction by mask with sevoflurane was significantly faster (210 ± 57sec, mean ± SD) than induction by isoflurane (264 ± 75sec)(Lerche *et al.* 2002). An earlier study described satisfactory induction of anaesthesia in cats with 8% sevoflurane in 33% oxygen, 66% nitrous oxide, the cats usually able to be placed in lateral recumbency within 1min (Tzannes *et al.* 2000). Two studies have investigated speed of induction in cats placed in induction chambers. One study showed significantly shorter time to intubation using 2.7.MAC doses of sevoflurane in comparison to isoflurane (434 ± 66sec vs 515 ± 69sec)(Imai *et al.* 2003). However, a similar study using 5% isoflurane and 8% sevoflurane showed no significant difference in time to intubation (Ko *et al.* 2001).

Two studies have evaluated whether human anaesthetists were able to reliably discern whether they were using halothane or sevoflurane to mask induce children, the agent being randomly allocated and vaporiser hidden from view. In one study, only the staff anaesthetists and not the anaesthesia residents were able to discern the agent

used (Morimoto *et al.* 2000). The group of anaesthetists in the second study were not able to reliably discern the agent used (Bacher *et al.* 1997).

In a multisite case series report comparing quality of induction of anaesthesia using sevoflurane with other standard anaesthesia protocols, no significant differences were found between groups (Branson *et al.* 2001). However, this study was limited by variation in the protocols employed for premedication and induction, with a large number of operators involved, potentially decreasing the ability to detect differences between the groups.

1.1.4.3 Recovery from anaesthesia

Summaries of data from humans indicate more rapid recovery from anaesthesia induced and maintained with sevoflurane than with halothane in children, based on time to extubation and psychomotor testing (Patel and Goa 1996). Likewise, recovery from sevoflurane anaesthesia in adult humans is generally faster than that from isoflurane anaesthesia (Patel and Goa 1996).

In unpremedicated dogs mask induced with isoflurane or sevoflurane, no significant differences could be found in any recovery variable, with extubation in a mean of 5.9 and 6.4min respectively, and most recoveries rated as "excellent" (Johnson *et al.* 1998). Neither could significant differences be found between recoveries in dogs anaesthetised using halothane, isoflurane or sevoflurane after induction with propofol (Polis *et al.* 2001).

1.1.5 Side effect profile

1.1.5.1 Effects on cerebral function

The effect of halogenated anaesthetics, measured in terms of EEG function, is somewhat two-pronged. Generally, a dose-dependent depression and slowing of activity is seen, progressing to isoelectricity (Modica *et al.* 1990). However, many of the volatile anaesthetics, and particularly those containing an ether linkage, are also associated with proconvulsant properties (Modica *et al.* 1990).

Halothane alone has not been reported to cause seizures in humans or dogs, although there are sporadic reports of seizure activity in humans when it is

administered with nitrous oxide (Modica *et al.* 1990; Steffey 1995). Isoflurane has not been reported to induce EEG evidence of seizure at any level of anaesthesia, either in human or dog (Scheller *et al.* 1990; Rampil *et al.* 1991).

There are no reports of seizures in dogs associated with sevoflurane. Healthy dogs anaesthetised with up to 2.5.MAC sevoflurane showed no EEG evidence of seizure, when exposed to hypocapnia and/or intense auditory stimuli (Scheller *et al.* 1990). However, two of 13 cats anaesthetised with this agent showed EEG evidence of seizure activity, provoked by electrical stimulation (Osawa *et al.* 1994). There are several case reports of seizures in non-epileptic and epileptic humans associated with sevoflurane anaesthesia (Adachi *et al.* 1992; Terasako and Ishii 1996; Woodforth *et al.* 1997; Kaisti *et al.* 1999; Iijima *et al.* 2000). Mask induction of non-epileptic humans with sevoflurane in a mixture of O_2 and N_2O revealed EEG evidence of seizure activity, with a heart rate increase of at least 30% being consistently associated with the seizure activity (Yli-Hankala *et al.* 1999). It may be questioned as to what electrical activity may be occurring in the canine brain during mask induction with sevoflurane, given the heart rate increases that are often recorded (*Section 1.1.5.2.1*). Unfortunately, these responses have not been studied in detail.

1.1.5.2 Effects on the cardiovascular system

1.1.5.2.1 Effects on heart rate

Mask induction of general anaesthesia in dogs using isoflurane or sevoflurane causes significant elevations in heart rate from baseline values (Mutoh *et al.* 1995). In contrast, inductions with halothane are not accompanied by significant changes in heart rate. These patterns persist throughout the maintenance phase of anaesthesia with the respective agents (Harkin *et al.* 1994; Mutoh *et al.* 1995; Mutoh *et al.* 1997; Polis *et al.* 2001), the elevations with isoflurane and sevoflurane being in the order of 30-40% with expired agent concentrations equivalent to 1.0.MAC to 2.0.MAC. However, one study showed decreases in heart rate with inspired concentrations of up to 3% sevoflurane (Yamada *et al.* 1994).

1.1.5.2.2 Effects on cardiac rhythm

Halothane's predilection for lowering the threshold to catecholamine-induced cardiac arrhythmias was one of the major motivations for further development of inhalant anaesthetics (Wallin *et al.* 1975; Steffey 1995). The plasma adrenaline (epinephrine) concentrations required to produce arrhythmias were established to be 39.1, 149.2, and 275.7ng.ml^{-1} for halothane, isoflurane and sevoflurane respectively (Imamura and Ikeda 1987). The use of thiobarbituates for induction of anaesthesia lowers the arrhythmogenic threshold concentration (Atlee and Malkinson 1982; Hayashi *et al.* 1988). Arrhythmogenic concentrations of adrenaline for the latter two agents result in marked hypertension (Imamura and Ikeda 1987; Hayashi *et al.* 1988).

1.1.5.2.3 Effects on cardiac contractility

Halothane, isoflurane and sevoflurane are all associated with depression of most measurable indicators of cardiac contractility in the dog (Bernard *et al.* 1990; Harkin *et al.* 1994; Mutoh *et al.* 1995; Mutoh *et al.* 1997). These agents cause a decrease in the concentration of free Ca^{2+} available within the myocardial cells (Bosnjak *et al.* 1988), reducing the strength of contraction of which the cell is capable. This decrease in Ca^{2+} concentration is due to slowing of the influx of Ca^{2+} through the sarcolemma (Bosnjak *et al.* 1988), decreases in Ca^{2+} accumulation in the sarcoplasmic reticulum (Su and Kerrick 1979), and decreases in contractile protein sensitivity to Ca^{2+} (Su and Bell 1986).

The depression of three important cardiac variables was almost identical during 2.MAC isoflurane or sevoflurane anaesthesia in dogs (Bernard *et al.* 1990). Cardiac output decreased by 17 ± 6% (mean ± SE), stroke volume decreased by 48 ± 4%, and left ventricular rate of pressure change (dP/dt) dropped by 61 ± 10%. Cardiac output and stroke volume were lower in dogs anaesthetised with 2.0.MAC halothane than in dogs anaesthetised with the equivalent level of isoflurane (Steffey and Howland 1978). However, no significant differences in cardiac index or stroke index were found in dogs anaesthetised with halothane, isoflurane or sevoflurane in a more recent study (Mutoh *et al.* 1997). Echocardiographic measurements during mask induction of anaesthesia with halothane or sevoflurane in children revealed

significantly less depression of left ventricular shortening fraction and velocity of circumferential fibre shortening with sevoflurane (Holzman *et al.* 1996).

1.1.5.2.4 Effects on diastolic function

Although most studies of cardiac performance focus on systolic variables, diastolic performance should not be ignored (Plotnick 1989; Grossman 1990). In contrast to halothane, anaesthesia with isoflurane or sevoflurane does not affect ventricular relaxation or chamber stiffness (Yamada *et al.* 1994), producing an improved preload with the newer agents.

1.1.5.2.5 Effects on vasculature

1.1.5.2.5.1 Systemic vasculature

Halothane, isoflurane and sevoflurane all cause systemic vasodilation at anaesthetic doses (Bernard *et al.* 1990; Malan *et al.* 1995; Mutoh *et al.* 1995; Holzman *et al.* 1996; Mutoh *et al.* 1997). Isoflurane and sevoflurane produce a similar degree of vasodilation (Bernard *et al.* 1990; Malan *et al.* 1995; Mutoh *et al.* 1995; Mutoh *et al.* 1997), generally greater than that produced by halothane (Pagel *et al.* 1991; Holzman *et al.* 1996), although results of some studies do not concur (Mutoh *et al.* 1995; Mutoh *et al.* 1997).

1.1.5.2.5.2 Coronary vasculature

Coronary vasculature is also dilated by these agents (Bernard *et al.* 1990; Harkin *et al.* 1994; Hirano *et al.* 1995). Sevoflurane may prevent the induction of "coronary steal" which has been controversially attributed to isoflurane, by better regulation of coronary arteriolar diameter (Mayer *et al.* 1991). "Coronary steal" refers to the preferential perfusion of normal areas of myocardium at the expense of those with stenosed vasculature, occurring after administration of a coronary vasodilator. It has only been recorded in the dog in the experimental setting (Blanck and Lee 1994).

1.1.5.2.5.3 Cerebral vasculature

In suppressing cerebral neuronal activity, volatile anaesthetics induce a dose-dependent decrease in the cerebral metabolic requirement for oxygen ($CMRO_2$) of about 30% in the case of isoflurane and sevoflurane (Scheller *et al.* 1990). Vasodilation of the cerebral vessels caused by halothane leads to increased cerebral blood flow (CBF) and intracranial pressure (ICP) (Steffey 1995; Patel and Goa 1996; Eger *et al.* 2002). Increased ICP may be deleterious to animals with intracranial pathology. In contrast, isoflurane and sevoflurane may retain these values within normal ranges (Scheller *et al.* 1990; Kuroda *et al.* 1997; Monkhoff *et al.* 2001). CBF is normally tightly regulated by homeostatic mechanisms and coupled to $CMRO_2$. This regulation is probably retained with 1.5.MAC isoflurane and sevoflurane anaesthesia (Kuroda *et al.* 1997).

1.1.5.2.6 Effects on blood pressure

Arterial blood pressure is a product of systemic vascular resistance and cardiac output (Ebert *et al.* 1995). Although mean arterial pressure (MAP) is generally higher with halothane than with equipotent doses of isoflurane or sevoflurane in humans, dogs or horses, establishing significant differences has been difficult given the small groups involved in most studies (Bernard *et al.* 1990; Frink *et al.* 1992a; Murray *et al.* 1992; Harkin *et al.* 1994; Malan *et al.* 1995; Mutoh *et al.* 1995; Holzman *et al.* 1996; Mutoh *et al.* 1997; Grosenbaugh and Muir 1998). A decrease in MAP of approximately 20% at 1.5.MAC is routinely found for each of the agents. Sevoflurane and isoflurane realise lower MAP values due to their greater vasodilation relative to halothane (*Section 1.1.5.2.5*).

In human patients, MAP following induction with propofol and maintenance with sevoflurane was lower than that following induction by mask with sevoflurane (Smith *et al.* 1992).

1.1.5.3 Effects on the Respiratory System

1.1.5.3.1 Odour and Irritancy

Halothane is described as having a “sweet” or “pleasant” odour (Dale and Brown 1987; Quail 1989). Sevoflurane is likewise endowed with a “pleasant” smell (Wallin *et al.* 1975; Patel and Goa 1996). The smell of isoflurane, on the other hand, is described as “pungent, ethereal” (Quail 1989), or “unpleasant” (Dale and Brown 1987).

The pungency of isoflurane often ruled out its use for mask induction in children, and halothane was used for this purpose until the introduction of sevoflurane (Agnor *et al.* 1998; Feiss 2000). A study in humans showed sevoflurane to have the least effect on respiratory system function during mask inhalation, causing no coughing or change in respiratory rate or functional residual capacity (Doi and Ikeda 1993). Halothane was the second least irritant agent, whilst isoflurane was the most irritant.

Administration of inhalants to the upper airways of dogs intubated *via* tracheotomy showed significant decreases in respiratory rate, tidal volume and minute ventilation with isoflurane, whilst there were no significant changes with sevoflurane (Mutoh *et al.* 2001). These isoflurane-related changes were ablated by nebulisation of lignocaine, supporting the suggestion that upper airway irritation is an important mediator of the respiratory system changes recorded during induction with isoflurane.

1.1.5.3.2 Respiratory effects post-induction

Halothane is the least respiratory depressant of the three inhalant agents in the dog (Mutoh *et al.* 1995; Steffey 1996; Mutoh *et al.* 1997). All three cause a decrease in ventilation, measured in terms of minute expired ventilation and arterial CO_2 (Mutoh *et al.* 1995; Mutoh *et al.* 1997). Isoflurane and sevoflurane showed a similar degree of respiratory depression, though only sevoflurane was significantly worse than halothane (Mutoh *et al.* 1997). Nevertheless, increases of arterial CO_2 to approximately 45mmHg at doses equal to 1.5.MAC indicate only a moderate degree of respiratory depression even with the two newer agents.

Halothane is significantly more effective at inhibiting bronchoconstriction following antigen or histamine challenge in the dog when compared to either isoflurane or sevoflurane (Yamakage *et al.* 1993).

Hypoxic pulmonary vasoconstriction occurs in the normal animal to divert pulmonary blood flow away from areas of unventilated lung to maximise gas

exchange. *In vitro*, inhalant anaesthetics blunt this response, in line with their generalised vasodilatory effects (Ishibe *et al.* 1993). However, this seems not to be clinically significant at normal doses in vivo, with the response to hypoxia preserved (Okutomi and Ikeda 1990; Eger *et al.* 2002).

1.1.5.4 Effects on renal function

In rats, halothane has been shown to produce a decrease in renal blood flow; the percentage of cardiac output perfusing the kidneys in unchanged (Crawford *et al.* 1992). Sevoflurane produced no change in renal blood flow in this study. However, in the dog, halothane and isoflurane produced no change in flow to the renal cortex (Gelman *et al.* 1984).

Degradation of inhaled anaesthetics releasing inorganic fluoride has potential for nephrotoxicity (Mazze *et al.* 1971). Quantities of fluoride produced during halothane and isoflurane anaesthesia do not approach toxic concentrations (Fee and Thompson 1997). Sevoflurane, however, is notably metabolised in the liver to produce inorganic fluoride at concentrations which may approach or even exceed the suggested toxic threshold for humans of 50μM in plasma (Kazama and Ikeda 1991; Kobayashi *et al.* 1992; Frink *et al.* 1994; Eger *et al.* 1997a; Eger *et al.* 1997b). Such plasma fluoride concentrations produced high output renal failure in humans (Mazze *et al.* 1971; Cousins and Mazze 1973) and rats (Cousins *et al.* 1974) following anaesthesia with the older inhalant agent methoxyflurane. However, despite the application of an enormous research effort, no evidence of postoperative renal compromise in terms of renal concentrating ability or blood urea concentrations has been found after sevoflurane anaesthesia (Higuchi *et al.* 1995; Bito *et al.* 1997; Eger *et al.* 1997a; Eger *et al.* 1997b; Kharasch *et al.* 1997; Ebert *et al.* 1998; Higuchi *et al.* 1998; Nishiyama and Hanaoka 1998; Mazze *et al.* 2000; Goeters *et al.* 2001). This may be due to the fact that sevoflurane degradation primarily occurs in the liver whereas methoxyflurane degradation occurs in the kidneys themselves (Kharasch *et al.* 1995).

Furthermore, sevoflurane degrades in strongly basic environments to produce several compounds, for simplicity labelled Compounds A-E (Patel and Goa 1996). Compound A, a vinyl ether, is the most important of these, produced when sevoflurane interacts with common carbon dioxide absorbents (Cunningham *et al.*

1996). Inspired concentrations of Compound A of greater than 50ppm were nephrotoxic to rats (Keller *et al.* 1995). These concentrations may be produced during human anaesthesia with sevoflurane, particularly when high sevoflurane concentrations and low fresh gas flow rates are used (Eger *et al.* 1997a; Eger *et al.* 1997b; Kharasch *et al.* 1997; Goeters *et al.* 2001). However, as mentioned previously, no evidence of decreased renal concentrating ability or increased blood concentrations of urea or creatinine have been noted following sevoflurane anaesthesia. This may be due to a lower activity in the human kidney of the enzyme *β*-lyase, which converts Compound A to more toxic metabolites in the rat kidney (Keller *et al.* 1995; Patel and Goa 1996).

There have been no reports relating to the effects of degradation of sevoflurane in dogs.

1.1.5.5 Effects on the liver

Blood and oxygen flow to the liver is decreased with anaesthetic doses of halothane (Frink *et al.* 1992b), the reductions being marked at 1.5 and 2.0.MAC. Both hepatic arterial flow and portal vein flow is reduced with this agent. Isoflurane and sevoflurane are associated with maintenance of hepatic arterial blood flow to at least 1.5.MAC (Bernard *et al.* 1992; Frink *et al.* 1992b), although portal vein flows decrease. However, the reductions reported with halothane are not considered to have clinical consequences in the absence of complicating factors such as hypoxaemia or systemic disease (Steffey 1995).

Halothane, isoflurane and sevoflurane all undergo biotransformation *in vivo*, primarily in the liver (Fee and Thompson 1997). Approximately 20-25% of inspired halothane is recovered as metabolites, whereas only 0.17% and 3% of isoflurane and sevoflurane respectively are biotransformed (Steffey 1995).

Halothane has been widely reported to cause hepatic injury in people (Ray and Drummond 1991; Fee and Thompson 1997; Eger *et al.* 2002). The most severe form is a fulminant hepatitis with high mortality, reported most commonly after repeated administrations (Ray and Drummond 1991). The aetiology of this syndrome (or syndromes) probably includes metabolic and immunological effects (Fee and Thompson 1997). There is a case report of similar pathology following halothane

anaesthesia in a series of goats (O'Brien *et al.* 1986). This syndrome has not been reported in the dog.

Isoflurane and sevoflurane have both been linked to hepatotoxicity in humans, although, in line with their greater biostability, the prevalence is far lower (Sinha *et al.* 1996; Turner *et al.* 2000; Bruun *et al.* 2001). As discussed above (*Section 1.1.5.4*), sevoflurane degradation releases inorganic fluoride ion, although this seems not to be of clinical significance. There are no case reports of isoflurane or sevoflurane hepatotoxicity in animals.

1.1.6 Hazards of occupational exposure

Similar to its hepatic effects in patients, halothane may cause decreased hepatic function in staff members exposed to the agent incidentally (Byhahn *et al.* 2001). Isoflurane and sevoflurane are not thought to cause hepatic pathology in those chronically exposed to low concentrations.

Halothane has been shown to be teratogenic in rats, mice and hares exposed to conditions similar to a poorly ventilated operating theatre (Byhahn *et al.* 2001). Mask inductions markedly increase the concentrations present in the theatre atmosphere, which may exceed recommend legislated limits (Hoerauf *et al.* 1997; Hoerauf *et al.* 1999). Minimal examination of the teratogenicity of isoflurane has been undertaken, and none for sevoflurane. No similar studies have been performed in the clinical veterinary environment.

1.1.7 Environmental effects

As halogenated compounds, halothane, isoflurane and sevoflurane have the potential to contribute to breakdown of the stratospheric ozone layer and "greenhouse effect". Normal practice in veterinary and human anaesthesia is to vent these inhalant anaesthetics to the atmosphere without modification. Global production of these agents has been estimated at 10kilotons per year (Langbein *et al.* 1999). Laboratory analysis and computer modelling suggests halothane has an ODP (Ozone Depletion Potential) of 1.56, with CFC-11 as a reference value of 1.00. The ODP for isoflurane and sevoflurane is 0.03 and 0.00 respectively (Langbein *et al.* 1999). Halothane's high value is due to its bromine content, whilst sevoflurane evades ozone depletion due to

its lack of either bromine or chlorine. Values for GWP (Greenhouse Warming Potential) suggested for halothane, isoflurane and sevoflurane are 0.02, 0.05 and 0.02, where CFC-12 is the reference of 1.00 (Langbein *et al.* 1999). These calculations led to the approximation that 0.03% of global warming is likely due to halogenated anaesthetics. The impact of these agents will decrease as halothane use in human anaesthesia decreases.

1.2 Propofol

1.2.1 Composition

Propofol is an intravenous anaesthetic agent, a derivative of phenol, chemically described as 2,6-diisopropylphenol. It was first synthesised in the early 1970's. It is insoluble in water. Initially, it was solubilised in Cremophor EL, but the high incidence of anaphylactoid reactions associated with this solvent led to its reformulation in an emulsion containing soybean oil, glycerol, egg lecithin and sodium hydroxide (Reves *et al.* 1994; Branson 2001). This emulsion contains no preservative, and will support bacterial and fungal growth (Bryson *et al.* 1995). Concern over outbreaks of infection traceable to contaminated propofol led to one manufacturer adding EDTA to the emulsion, which seems to have been effective in halting such outbreaks (Shafer 2002).

1.2.2 Pharmacokinetics

The pharmacokinetics of propofol in dogs best fits a two compartment open model (Zoran *et al.* 1993). Distribution to the CNS is rapid, followed by a slower elimination that relies heavily on metabolism. However, redistribution to tissues such as muscle probably accounts for most of the decrease in plasma concentration required for termination of propofol's hypnotic effects (Zoran *et al.* 1993). In mixed-breed dogs given a single induction bolus of propofol for endotracheal intubation, recovery to sternal recumbency and to standing occurred at plasma propofol concentrations of 0.753 ± 0.484 and 0.676 ± 0.338$\mu g.ml^{-1}$ respectively. Mean plasma concentrations at 60min post-induction were 0.161 ± 0.059$\mu g.ml^{-1}$ in mixed breed dogs (Zoran *et al.* 1993), indicating a concentration well below that expected to influence recovery if anaesthesia was maintained with a gaseous agent. In this study, greyhounds showed notably slower recoveries, with higher peak plasma propofol concentrations and recovery occurring at higher plasma concentrations. This is likely due to differing body composition, and a lower capacity for hepatic metabolism.

1.2.3 Metabolism

Hepatic metabolism is undoubtedly significant in propofol-anaesthetised patients, but other sites are involved (Zoran *et al.* 1993). Humans undergoing hepatic transplant were able to metabolise propofol to a similar degree when no liver blood flow was present (Veroli *et al.* 1992). Metabolites are primarily excreted in the urine (Bryson *et al.* 1995).

1.2.4 Induction of and recovery from anaesthesia

Propofol induces general anaesthesia when administered by intravenous injection, generally as a single bolus. Early described doses to allow endotracheal intubation in unpremedicated dogs ranged from 5.2 ± 2.6mg.kg^{-1} (Weaver and Raptopoulos 1990) to 6.55 ± 1.7mg.kg^{-1} (Morgan and Legge 1989). Premedication with various agents, most commonly acepromazine, lowered these doses to 3.6 ± 1.4 and 4.5 ± 1.53 mg.kg^{-1} respectively. Apnoea of up to 30sec duration has been noted commonly upon induction (Watkins *et al.* 1987; Morgan and Legge 1989; Short and Bufalari 1999). Slowing the rate of administration appears to decrease the incidence of this complication (Watkins *et al.* 1987). Induction is generally quiet, smooth and excitement-free (Watkins *et al.* 1987). Lower doses of propofol for endotracheal intubation may in turn require supplementary boluses if anaesthesia is to be maintained using inhalants, due to the rapid clearance of propofol (Weaver and Raptopoulos 1990).

Recovery after a single induction bolus of propofol was judged complete in 18 ± 7min in unpremedicated dogs, and 22 ± 10min in dogs premedicated with low doses of acepromazine (Watkins *et al.* 1987). Mixed breed, unpremedicated dogs stood after 14.63 ± 3.6min in another study, whereas greyhounds took 21.7 ± 3.3min (Zoran *et al.* 1993). Recovery after a two hour continuous infusion of propofol was similar to an equivalent period of isoflurane anaesthesia, with extubation in a mean of 13.5min, compared to 12.7min after isoflurane (Keegan and Greene 1993).

1.2.5 Side effects profile

1.2.5.1 Cardiovascular effects

Mild elevations in heart rate are commonly reported during induction of anaesthesia with propofol, however these do not reach statistical significance in most studies (Hall and Chambers 1987; Ilkiw *et al.* 1992; Bufalari *et al.* 1997). A drop over time may occur in dogs maintained by constant infusion of propofol (Hall and Chambers 1987; Keegan and Greene 1993). The presence of a stable heart rate despite a significant drop in arterial blood pressure was theorised to be due to a resetting of the baroreceptor reflex (Cullen *et al.* 1987), although more recently direct depression of baroreceptor response by propofol has been demonstrated (Sellgren *et al.* 1994).

Induction doses of propofol in the dog are associated with a decrease in cardiac output that approaches 20% one minute after administration. Propofol has direct effects on myocardial contractility, decreasing maximum left ventricular force by 15-20% (Brussel *et al.* 1989; Pagel and Warltier 1993). A similar degree of depression of systolic and diastolic blood pressure is reported (Brussel *et al.* 1989). A simultaneous decrease in systemic vascular resistance of 11.6% occurs, predominantly due to effects on arteries and arterioles rather than capacitance vessels. Moderate hypovolaemia does not change the degree of these effects (Ilkiw *et al.* 1992). These variables rebound close to baseline values by five minutes after administration (Brussel *et al.* 1989; Ilkiw *et al.* 1992).

1.2.5.2 Respiratory effects

Apnoea upon administration is a common side-effect noted with propofol (Watkins *et al.* 1987; Morgan and Legge 1989; Keegan and Greene 1993; Zoran *et al.* 1993; Short and Bufalari 1999). This is noted to be transitory in nature, undoubtedly linked to the rapid clearance of propofol. Injection over up to 40sec., and giving to effect rather than a predetermined dose, minimise this effect (Watkins *et al.* 1987).

Commensurate with this often reported complication on induction is respiratory depression throughout the period of anaesthesia. Arterial CO_2 is increased, although whilst this increase is statistically significant, it may not be biologically significant, with a rise to 41.9mmHg from 34.6mmHg five mintues after induction in one study of mixed breed dogs (Robertson *et al.* 1992). Respiratory rate decreases

moderately (Robertson *et al.* 1992). The respiratory effects of a continuous infusion of propofol for general anaesthesia are similar in magnitude to isoflurane anaesthesia (Keegan and Greene 1993).

1.2.5.3 Proconvulsant/anticonvulsant effects

Propofol has been associated with seizure activity in humans. This includes whole-body tonic-clonic seizure activity and abnormal movements (Makela *et al.* 1993; Borgeat 1997). These are most commonly, though not exclusively associated with induction of anaesthesia. These are more commonly seen in patients with pre-existing epilepsy (Makela *et al.* 1993; Bryson *et al.* 1995). However, there is a suggestion that these events are subcortical in origin, and therefore should not be considered epileptic (Borgeat 1997). Involuntary movements, trembling or even mild tonic-clonic activity are noted to occasionally occur during or after induction of anaesthesia with propofol in dogs, and may last for the duration of anaesthesia (Weaver and Raptopoulos 1990; Robertson *et al.* 1992; Zoran *et al.* 1993). No studies of the canine electroencephalogram during these complications have been undertaken. None of the reports of such activity in dogs note any postoperative neurologic deficits in these animals.

Propofol has also been shown to have anticonvulsant properties. It has been successfully used to treat seizures of intracranial origin and following portosystemic shunt surgery in dogs (Heldmann *et al.* 1999; Steffen and Grasmueck 2000). The doses required may be so low as to allow the animal to eat and drink whilst on a constant rate infusion of propofol. Status epilepticus in the human has also been treated with propofol (Borgeat 1997).

The exact means of action for these effects of propofol is unknown. Unlike thiobarbituates, in which antiepileptic action is mainly mediated by the GABA receptor, propofol causes a more uniform depression of CNS activity (Borgeat 1997).

1.3 Acepromazine

1.3.1 Introduction

Acepromazine (ACP) is a derivative of the compound phenothiazine, chemically described as 2-acetyl-10-(3-dimethylaminopropyl) phenothiazine. Its tranquillising properties make it a common choice of premedicant for anaesthesia in the dog. It has been in veterinary use since the early 1960's. Phenothiazine derivatives are classed as neuroleptics due to both their tranquillising effects and their ability to modify psychotic behaviours in humans (Gross 2001).

1.3.2 Method of action

Phenothiazine and its derivatives act primarily through blocking dopamine in the central nervous system (CNS), and the effects of dopamine and other catecholamines in the periphery. Following administration, the rate of dopamine turnover in the brain is increased (Hornykiewicz 1973; Matthysse 1973). Brain stem activity is depressed, as are the connections to the cerebral cortex (Pugh 1964; Gross 2001).

In the periphery, catecholamine function, most specifically α-adrenergic function, is blocked by ACP and other phenothiazines. This property elicits most of the cardiovascular side-effects of ACP.

1.3.3 Therapeutic effects

Although the term sedation is sometimes used to describe the effects of ACP, tranquillisation is perhaps more accurate. Tranquillisation refers to "*a state of sedation not accompanied by the lethargy and apathy associated with most sedatives. Tranquillisation proper need not be objectively detectable, because the motor cortex need not be markedly depressed*" (Pugh 1964).

Published intramuscular doses used for producing tranquillisation in dogs vary from 0.04mg/kg (Rutherford 1983) to 1.0mg/kg (Popovic *et al.* 1972). Lower doses have gained popularity in more recent times, particularly in combination with other drugs. Rutherford (1983) coined an often repeated suggestion to use no more than

3.0mg total dose per dog, and even lower doses in large dogs, although the basis for this recommendation was not elucidated. The effects produced include changes to the skin of the face, with looser, wrinkled skin over the frontal bones, drooping of the upper eyelid and protrusion of the nictitating membrane (Pugh 1964). "Voluntary" recumbency follows signs of posterior in-coordination. Dogs become more amenable to handling. These effects appear to abate after about 3-4hr (Pugh 1964).

The use of ACP alone decreases anaesthetic requirements both for induction with agents such as thiopentone (Pugh 1964; Raiha *et al.* 1989) and inhalants such as halothane (Raiha *et al.* 1989), with a 0.04mg/kg IM dose decreasing the halothane MAC by 46% (Heard *et al.* 1986).

ACP also acts as an anti-emetic (Valverde *et al.* 2003), and is effective in raising the threshold for catecholamine-induced ventricular fibrillation in dogs anaesthetised with thiamylal and halothane (Muir *et al.* 1975).

Most studies of the effects of ACP have used it in combination with various opioids, a combination known as neuroleptanalgesia (Gross 2001). Such opioids include oxymorphone and butorphanol. As well as adding analgesia, which is effectively absent with ACP alone (Barnhart *et al.* 2000a), these combinations show longer duration of action and should decrease the dose requirement of ACP (Barnhart *et al.* 2000a).

1.3.4 Side effects profile

Due primarily to its α-adrenergic antagonist action, ACP causes vasodilation and subsequent hypotension in the dog. Doses of up to 1.1mg/kg intravenously or intramuscularly (Popovic *et al.* 1972) produced approximately a 15% decrease in MAP over 2hr, whilst intramuscular doses of 0.11mg/kg caused decreases of approximately 20% in MAP (Turner *et al.* 1974). A combination of acepromazine with butorphanol reflected similar decreases in MAP as a measure of cardiovascular function (Kojima *et al.* 1999). However, other studies have shown no significant changes in MAP after doses in combination with butorphanol or oxymorphone (Cornick and Hartsfield 1992). Cardiac index did not change in halothane anaesthetised dogs given 0.2mg/kg ACP IM (Boyd *et al.* 1991).

Heart rate may decrease mildly when using ACP (Popovic *et al.* 1972; Boyd *et al.* 1991; Kojima *et al.* 1999).

Kidney function, measured in terms of glomerular filtration rate, is not affected by these reductions in arterial pressure (Newell *et al.* 1997).

An often repeated suggestion regarding ACP is its ability to decrease the ictal threshold. This has not been studied. An aetiology suggested by Gross (2001) is stimulation of extrapyramidal motor pathways.

Also due to α-adrenergic vasodilation, body temperature drops as more blood flow is directed to the periphery rather than the body core (Pugh 1964).

1.4 Morphine

1.4.1 History and derivation

Morphine is the principal alkaloid of opium, which in turn is the dried form of the exudate of the poppy plant (*Papaver somniferum*). Powdered opium contains approximately 10% anhydrous morphine (Branson and Gross 2001).

Opium has been used for the relief of pain since at least the dawn of recorded history, and its properties were well known to Greek, Roman and Arabian physicians. In 1680, Sydenham wrote: "*Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal or so efficacious as opium*" (Hodgson 2000). Exported to the Far East in the 18th and 19th centuries, the economic potential of addiction to opium led to the "Opium Wars", which, despite increasingly vigorous regulation of the trade, have never fully ceased.

Morphine was first derived from opium by F.W.A. Sertűrner in 1805, who named it after Morpheus, the Greek god of dreams (Branson and Gross 2001).

1.4.2 Pharmacology

The primary salt of morphine is morphine sulfate, and this is the form most commonly administered to animals (Thurmon *et al.* 1996; Barnhart *et al.* 2000b; Branson and Gross 2001). Opium derivatives act on opioid receptors, which are found in all parts of the nervous system and many peripheral tissues. The receptor subtype defined by its affinity for morphine is the μ (Mu) receptor (Reisine and Pasternak 1996), although morphine will also have some effects at κ (Kappa) receptors, particularly at higher doses. Mu receptors have been further subclassified into μ_1 and μ_2 types, the unwelcome side effects suspected as being involved with the μ_2 receptor, although both mediate analgesia (Branson and Gross 2001). The disposition of morphine is not affected by halothane or isoflurane anaesthesia (Steffey *et al.* 1993).

Morphine is generally delivered to the dog via parenteral routes. Intramuscular administration leads to variable but generally high plasma concentrations compared to administration either orally or rectally. Bioavailability is less than 20% for oral or rectal administration. Intravenous administration is also commonly used (Vatner *et al.*

1975; Barnhart *et al.* 2000b; Branson and Gross 2001), although histamine release and excitation is a concern (*Section 1.4.4*).

Being a full μ opioid agonist, morphine does not exhibit an appreciable "ceiling" to its effects, which is beneficial for patients in extreme pain (Branson and Gross 2001).

1.4.3 Therapeutic effects

Analgesia is the primary therapeutic effect of morphine. The peak of action after subcutaneous or intramuscular administration of 0.1 to 0.5mg.kg^{-1} requires 30 to 45min (Branson and Gross 2001), and may last 3 to 4hr, although this is undoubtedly dependent upon the level of noxious stimulation. Much higher doses have been administered, however not for the purposes of studying analgesia.

Sedation may or may not be considered a therapeutic effect of morphine. Doses of up to 0.5mg.kg^{-1} have been administered for this purpose; such doses given SC or IM avoid the excitation seen at higher doses. In combination with acepromazine, this neuroleptanalgesia is useful as premedication for anaesthesia, or for procedures such as ultrasonography (Della Torre *et al.* 2000).

Administration of morphine has a significant effect on requirements for inhaled anaesthetics. MAC for halothane or isoflurane was decreased by 35-40% by intravenous morphine at 1.0mg.kg^{-1} IV, a dose much higher than that commonly used in practice (Steffey *et al.* 1993). A similar decrease was reported after epidural administration of 0.1mg.kg^{-1} morphine in the dog (Valverde *et al.* 1989). The MAC reduction associated with a combination of acepromazine and morphine has not been studied.

1.4.4 Side effects profile

Addiction *per se* is not generally an issue for canine patients, although physical dependence can occur after several doses of morphine (Martin *et al.* 1974).

Effects on the CNS vary widely between species. Manic effects, locomotor stimulation and dysphoria are common at low doses in many species, such as the cat, horse, pig, goat, cow and sheep (Branson and Gross 2001). Such excitation only occurs in dogs at high doses (Vatner *et al.* 1975; Robinson *et al.* 1988; Reisine and

Pasternak 1996; Branson and Gross 2001). This may include generalised seizures at extreme doses. In the dog, an initial rise in body temperature and subsequent hypothermia are attributed to direct effects on the thermoregulatory centre (Branson and Gross 2001).

Vomiting is a common side effect of morphine in dogs, generally occurring within 10min of parenteral administration. This would appear to be centrally mediated (Reisine and Pasternak 1996). A generalised increase in gastrointestinal tone, and uncoordinated peristalsis may precipitate constipation in the medium to longer term.

Endogenous opiates are thought to have important regulatory roles in the cardiovascular system (Reisine and Pasternak 1996). Morphine at 0.5mg.kg^{-1} IV induces a transient decrease in blood pressure and increase in heart rate in the dog. Blood pressure returns soon to baseline, and heart rate drops significantly due to vagotonic effects of the drug (DeSilva *et al.* 1978). Lower doses (0.015mg.kg^{-1} IV) may induce an initial increase in MAP (Given *et al.* 1986). The canine heart is significantly less prone to ventricular fibrillation under its influence (DeSilva *et al.* 1978). These effects appear to be centrally mediated. There is also significant vasoconstriction of canine coronary vasculature and reduction in coronary blood flow (Vatner *et al.* 1975). This is in sharp contrast to the human, where morphine has been commonly used to promote coronary blood flow.

Respiratory depression is a hallmark of opiate use. Intravenous morphine at 1.0mg.kg^{-1} caused an increase in arterial CO_2 from 42.2 and 46.2mmHg to 55.1 and 54.0mmHg under halothane and isoflurane anaesthesia respectively (Steffey *et al.* 1993). Respiratory depression is not an issue for conscious dogs given normal therapeutic doses of morphine (Branson and Gross 2001).

Histamine release is consistently recorded when high doses of morphine are delivered intravenously (Robinson *et al.* 1988). Whilst the histamine concentrations may be well in excess of those causing anaphylactice shock in humans, dogs do not seem to suffer the serious cardiovascular effects that should be associated with such a response.

1.5 Meloxicam

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID). It is a relatively new NSAID that is characterised by its more favourable side effect profile and prolonged action compared to older drugs of its class.

A primary effect common to NSAID is their suppression of the enzyme cyclo-oxygenase (COX). This enzyme metabolises arachidonic acid into precursors for several important mediators of the inflammatory process collectively referred to as the eicosanoids (Higgins and Lees 1984). Inactivation of this enzyme by NSAID inhibits many of the signs of inflammation (Vane 1971; Lascelles *et al.* 1998; Matthews *et al.* 2001). More recently, it has been elucidated that two isoenzymes of COX are present, labelled COX-1 and COX-2 (Donnelly and Hawkey 1997). Broadly speaking, COX-1 is responsible for the physiological mechanisms requiring production of eicosanoid substances such as prostaglandins, whereas COX-2 is induced in inflammatory situations. Suppression of both isoenzymes, as achieved with older NSAID such as aspirin, led to the typical side effects of gastrointestinal ulceration and renal toxicity in both the human and dog (Johnston and Budsberg 1997).

In theory, a NSAID which selectively inactivates COX-2 more than COX-1 should result in a decrease in deleterious side effects. Meloxicam is such a drug, being more selective for the inducible isoenzyme than other NSAID such as carprofen (Engelhardt *et al.* 1996a; Kay-Mugford *et al.* 2000). However, evidence of improved tolerability for a COX-2 selective NSAID is yet to be shown in the dog (Johnston and Budsberg 1997; Forsyth *et al.* 1998; Matthews *et al.* 2001).

Although inhibition of COX activity has been the primary focus of investigation into the method of action of NSAID for many years, it is clear that these drugs work in other ways, through both peripheral and central pathways (McCormack 1994; Cashman 1996). There is much still to be understood as to the action of these drugs.

Meloxicam has been shown to be superior to butorphanol for analgesia in dogs undergoing abdominal surgery (Matthews *et al.* 2001). No gastrointestinal or other side effects were noted on necropsy of these dogs. Meloxicam had no significant effect on cardiorespiratory variables measured in dogs anaesthetised with chloralose-urethane (Engelhardt *et al.* 1996b). The effect of meloxicam on MAC for dogs anaesthetised with gaseous agents has not been studied, however carprofen has no

effect on MAC of isoflurane or halothane in the dog (Alibhai and Clarke 1996; Ko *et al.* 2000). Meloxicam did not enhance the MAC reduction caused by morphine in the rat (Santos *et al.* 2004).

1.6 Conclusion

The fluorinated hydrocarbon inhalant anaesthetics have been the primary agents used for maintenance of general anaesthesia for the past fifty years, and are used in various situations for induction of anaesthesia. The development of isoflurane and more recently sevoflurane overcame some of the side effects seen with the older halothane. Whilst the biological effects of these agents have been in some areas extensively studied, there remains some unanswered questions, particularly in relation to the veterinary literature.

The efficacy of the three inhalants for induction of anaesthesia in humans has been thoroughly examined. These studies have compared the three agents both in terms of the speed of induction and the quality of induction. Experimental studies using volunteers have been undertaken, as well as large studies of clinical cases. The agents have been compared against each other; they have also been compared to induction of anaesthesia with intravenous agents such as propofol. However, the veterinary literature contains a fewer number of studies of induction of anaesthesia with these agents in the dog. The only previous studies to quantify and compare the speed and quality of induction with these agents have been undertaken in the experimental situation. The limited number of clinical studies have not attempted to compare the agents.

Likewise, recovery from anaesthesia with these agents has been more closely studied in the human than in the dog. Again, the only studies attempting to compare recovery after anaesthesia with these agents in the dog have been in the experimental environment, in animals not exposed to surgery.

Therefore, the current study was implemented to test the following hypotheses:

- Induction of general anaesthesia with sevoflurane would be faster and of better quality than that seen with either isoflurane or halothane.
- Induction of anaesthesia with sevoflurane would be of equivalent speed and quality to that seen with propofol.
- Recovery after sevoflurane anaesthesia would be faster and of better quality than that seen with either isoflurane or halothane.

- The use of acepromazine and morphine as premedication before anaesthesia would lead to a faster and smoother induction of anaesthesia.

Chapter 2: Materials and Methods

2.1 Study Objectives

The objectives of the study were as follows:

1. To compare the quality and speed of anaesthetic induction, maintenance and recovery with sevoflurane to those occurring with isoflurane and halothane, in healthy dogs undergoing routine desexing.
2. To compare the quality and speed of anaesthetic induction, maintenance and recovery using intravenous propofol for induction, and sevoflurane, isoflurane or halothane for maintenance, in healthy dogs undergoing routine desexing.

The characteristics of sevoflurane anaesthesia in the dog have been extensively studied in the experimental environment. This study aimed to redress the paucity of data related to its characteristics relative to the more established inhalant agents in the clinical environment.

2.2 Experimental design

The study was designed as a prospective clinical study. The dogs enrolled were young adult, healthy dogs scheduled for general anaesthesia and surgery for routine castration or ovariohysterectomy.

Each dog was placed into one of twelve groups that determined the anaesthetic protocol employed (*Table 2.1*). The first part of this process was an active selection as to whether the dog would receive premedication or no premedication. This decision was based on the assessment of demeanour described below (*Section 2.5.1.2.1*). Animals scoring 1 or 2 (more excited or nervous animals) were placed in a premedication group. Animals scoring 3 or 4 (calmer animals) were placed in a no-premedication group. From this point, group allocation was random, appointing an induction method – intravenous or inhalant – and maintenance inhalant agent –

halothane, isoflurane or sevoflurane. Those in which anaesthesia was induced with an inhalant anaesthetic agent were maintained on the same inhalant.

Maintenance agent ►	**Halothane**		**Isoflurane**		**Sevoflurane**	
Intravenous induction	NP	P	NP	P	NP	P
Inhalant induction	NP	P	NP	P	NP	P

Table 2.1 Experimental groups
NP = No Premedication
P = Premedication

One veterinarian (the author) undertook all anaesthetic inductions, and supervised the maintenance of and recovery from anaesthesia.

Dogs were enrolled from the Canine Desexing Clinic (CDC) operated by the Faculty of Veterinary Science, University of Sydney. The purpose of this clinic is to allow final year undergraduate students to gain experience in surgery and anaesthesia of small animals, under close supervision. The anaesthesia protocols used (*Section 2.3*) were those routinely undertaken in this clinic. Of the 8 to 10 animals presented each day of operation of the CDC, 1 to 3 dogs were enrolled in the study. The selection process involved enrolling the first, third and fifth dogs brought by the final year students from the kennel area to the induction area. The students were unaware of the nature of the study.

Young to middle aged adult dogs were enrolled. As exact ages for animals in the CDC were not known, an approximation was made from examination of the dogs' appearance, hair coat, eyes and teeth.

Cryptorchid dogs being desexed were included in the study, as were females undergoing desexing whilst in oestrus. However, animals undergoing any other form of non-routine desexing, or other concurrent procedures, were excluded.

Participants were considered healthy on the basis of a routine physical examination, as described below (*Section 2.5.1.1.1*).

2.3 Anaesthesia protocols

2.3.1 Premedication

Dogs selected into a premedication group received 0.03mg.kg^{-1} acepromazine[1] and 0.5mg.kg^{-1} morphine[2], injected into the lumbar musculature midway between the last rib and pelvis. These two drugs were drawn up in one suitably sized syringe[3], and injected through a 23Gx1"[4] or 25Gx⅝"[5] needle, the larger needle being used for dose volumes in excess of 1.0ml. Animals in the no-premedication groups were not given a placebo injection, to retain similarity to private practice.

After injection, premedicated animals were placed on a blanket on the floor and restrained by a leash. A heat lamp[6] was placed approximately one metre away from premedicated animals in both locations. Non-premedicated animals were held in similar conditions prior to anaesthetic induction, without the use of the heat lamp. Animals given premedication were not disturbed for at least twenty minutes following the injection.

From this point onwards, animals in the premedication and no-premedication groups were treated identically.

2.3.2 Intravenous catheterisation

Each dog had an intravenous catheter placed in either the right or left cephalic vein. Catheter size was selected by the supervising veterinarian, based on the size of the animal and the dimensions of the cephalic vein. Either a 20Gx1.16" or 22Gx1.00" intravenous catheter[7] was used, the smaller generally being used in dogs weighing less

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[1] A.C.P. 2. Delvet, Seven Hills, NSW, Australia

[2] Morphine Sulfate Injection BP 10mg/ml. David Bull Laboratories, Mulgrave, Victoria, Australia

[3] 1.0 and 3.0ml syringes: Terumo Syringe, Terumo (Phillipines) Corporation, Phillipines

[4] Terumo Needle, Terumo Corporation, Tokyo, Japan

[5] B-D PrecisionGlide Needle. Becton-Dickinson Medical (S) Pte Ltd. Singapore

[6] Osram Siccatherm Bulb 275W. Osram

[7] BD Insyte. Becton-Dickinson Medical (S) Pte Ltd. Singapore

than 10kg. A short T extension set[8] with injection port[9] was attached to the hub of the intravenous catheter, and the catheter/extension set was secured to the leg using adhesive tape[10]. The catheter was flushed with 0.9% saline[11] to which had been added 2IU.ml^{-1} heparin[12].

2.3.3 Induction protocols

2.3.3.1 Inhalant agent inductions

Inhalant inductions were undertaken using a single anaesthetic machine[13], with this same machine used for maintaining all cases under anaesthesia. This machine was equipped with a paediatric rebreathing circuit[14] for all dogs less than 10kg, and a human adult co-axial rebreathing circuit[15] for dogs in excess of 10kg. Carbon dioxide was removed from the circuit using soda lime[16]. The appropriate size for the rebreathing bag was considered to be that which fell within the upper and lower limits of the following formula:

Rebreathing bag size = (Tidal volume) x 5
Lower limit: (0.01 x (weight (kg)) x 5 (litres)
Upper limit: (0.02 x (weight (kg)) x 5 (litres)

The following rebreathing bag sizes were available: 0.5, 0.75, 1.0, 2.0, 3.0 litres[17].

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[8] Abbott Lifeshield Microbore Extension Set. Abbott Laboratories, North Chicago, IL, USA

[9] IN-Stopper. B.Braun Melsungen AG, Germany

[10] Kendall Curity Standard Porous Tape. The Kendall Company, Mansfield, MA, USA

[11] 0.9% Sodium Chloride. Baxter Healthcare Pty Ltd, Old Toongabbie, NSW, Australia

[12] Heparin Injection BP. David Bull Laboratories, Mulgrave, Victoria, Australia

[13] The Stinger. Advanced Anaesthesia Specialists, Gladesville, NSW, Australia

[14] Paediatric rebreathing circuit. Endovations, Leichhardt, NSW, Australia.

[15] Universal F2. King Systems Corporation, Noblesville, IN., USA.

[16] Drägersorb 800Plus. Dräger Medical AG & Co KGaA, Lübeck, Germany

[17] Ohmeda Medical, Laurel, MD, USA.

The selected inhalant was delivered from a vaporiser mounted[18] in an out-of-circuit configuration; halothane[19], isoflurane[20] and sevoflurane[21] were each delivered from a single vaporiser[22,23,24] throughout the study. Visualisation of the sight glass of each vaporiser ensured it was at least half full before each anaesthetic procedure was commenced. All three vaporisers had been calibrated within the twelve months prior to the commencement of data collection. Their output at each dial setting was measured at this calibration. Calibration was assessed again at the end of the data collection period.

All inhalant inductions were performed using a clear plastic mask[25] which covered the muzzle of the dog. The smallest mask which would accommodate the full muzzle was used. A rubber diaphragm surrounding the aperture of the mask improved the seal possible with the mask in place. The mask was not placed over the dog's muzzle until the commencement of the induction process. Between the mask and the patient connector of the circuit was placed an adaptor which provided a coupling for the sampling hoses of the capnograph and end-tidal anaesthetic agent monitor (*Section 2.5.3.1.2*). Before connection of mask and adaptor, the anaesthetic machine was checked for leaks by pressurising the circuit with oxygen using the emergency oxygen bypass valve. The machine was considered safe if the pressure on the machine mounted pressure gauge fell less than 5cmH_2O in 20seconds, from an initial 20cmH_2O.

Induction of general anaesthesia was undertaken with dogs on the floor of the induction area when they weighed in excess of 20kg. Patients less than 20kg were held on a table during induction. Smaller dogs were held by a veterinary nurse and the veterinarian administering the anaesthetic agent. For larger dogs an additional person

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[18] Selectatec vaporiser mount. BOC Australia, Annandale, NSW, Australia

[19] Rhodia Halothane. Merial Australia Pty Ltd, Parramatta, NSW, Australia

[20] Isoflo. Abbott Australasia, Kurnell, NSW, Australia

[21] SEVOrane. Abbott Australasia, Kurnell, NSW, Australia

[22] Halothane vaporiser: FluoTec 3, Cyprane, Keighley, England. Remanufactured by Advanced Anaesthesia Specialists, Gladesville, NSW, Australia

[23] Isoflurane vaporiser: IsoTec3. Cyprane, Keighley, England. Remanufactured by Advanced Anaesthesia Specialists, Gladesville, NSW, Australia.

[24] Sevoflurane vaporiser: Blease Datum Series B. Blease, Chesham Bucks, England

[25] Animal mask. GaleMed Corporation, Taiwan.

was enlisted to restrain the dog's hindquarters only when necessary. The minimum amount of restraint required was used, to minimise the stress on the patient.

At the point of commencement of the inhalant induction process, the oxygen[26] flow was switched on, and set to 3.0 $l.min^{-1}$. This flow rate ensured the anaesthetic concentration inspired by the patient approached the setting on the vaporiser as rapidly as possible, and minimised any rebreathing of expired air within the mask. The mask was immediately placed over the dog's muzzle and a stopwatch[27] was started at this time. At this stage, no anaesthetic agent entered the circuit, the aim being to increase the patient's oxygen reserve prior to anaesthetic administration. No nitrous oxide or other gases were used at any stage.

At two minutes after commencement, the anaesthetic vaporiser was switched on, directly to its maximum rated output. For the halothane and isoflurane vaporisers, this was 5.0%. For the sevoflurane vaporiser, the value was 8.0%. This output was maintained for the duration of the induction process, with no abatement of the vaporiser output until after endotracheal intubation.

The level of restraint upon the animal was increased only as needed to maintain the animal's head within the mask, though no means other than manual restraint were employed. If the dog withdrew its head from the mask, the mask was replaced over the muzzle immediately, with a minimum of additional restraint.

Inhalant induction was abandoned only after the animal had made at least three vigorous attempts to withdraw its head from the mask, combined with movements of the legs and torso, making restraint difficult or impossible, and showed obvious signs of distress. Such a patient was noted as an "abandoned inhalant induction" and anaesthesia was induced using propofol as per the intravenous induction protocol below (*Section 2.3.3.2*).

As the dog relaxed, it was placed into sternal recumbency in preparation for endotracheal intubation. Judgement of preparedness for endotracheal intubation was made by observing respiratory rate and pattern, eye movement and position, response to light tapping of the medial commissure of the eyelids (palpebral reflex), jaw tone and general muscle tone. When the administering veterinarian considered the animal

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[26] Oxygen Medical EP Grade. Air Liquide Healthcare Pty Ltd, Annandale, NSW, Australia

[27] Electronic Clock Timer. Tandy Australia, Regents Park, NSW, Australia

ready for endotracheal intubation, the oxygen flowmeter was turned off and the mask removed.

The veterinary nurse held the dog's mouth with one hand on the upper jaw and the other hand extending the tongue over the lower incisors. A laryngoscope[28] with a suitably sized blade was used to improve visualisation of the larynx, and an endotracheal tube of optimal diameter was selected and positioned. It was secured in place with gauze tape[29].

If the patient made one or more attempts to swallow or resist positioning during the intubation procedure, the laryngoscope was removed and the mouth closed. The induction mask was replaced over the dog's muzzle and the oxygen flowmeter reset to 3.0 $l.min^{-1}$. This was considered a failed intubation attempt. The patient was allowed to continue inhaling the induction agent until it again reached a level of anaesthesia considered suitable for endotracheal intubation, when intubation was again attempted.

Following successful endotracheal intubation, the induction mask was removed from the breathing circuit of the anaesthetic machine and the circuit connected to the endotracheal tube. Dogs induced on the floor were lifted onto the induction and surgical preparation table before being connected to the breathing circuit. Oxygen flow was recommenced at 3.0 $l.min^{-1}$, the vaporiser output remaining at the maximum rated output. The cuff of the endotracheal tube was filled with room air whilst the circuit was pressurised to 15cmH_2O until no gas leak around the endotracheal tube was audible.

The dog was maintained in sternal recumbency until the animal was sufficiently anaesthetised to be moved into lateral recumbency without causing undue stimulation. The decision as to when to decrease the vaporiser output was based on response to this movement, palpebral reflex and muscle tone of the jaw. When both jaw tone and palpebral reflex were considerably reduced or absent, vaporiser output was adjusted to a value twice the previously published MAC for that agent, rounded to the nearest 0.5%. This equated to 1.5% for halothane, 3.0% for isoflurane and 4.5% for sevoflurane. This vaporiser output was maintained for a further 5min, unless signs

[28] Laryngoscope. Heine Optical, Herrsching, Germany.

[29] Tensofix 5cm. Smith & Nephew Medical Fabrics Ltd, Brierfield, England

of unacceptably light anaesthesia were detected. A dose equivalent to 1.0mg.kg^{-1} of propofol was administered IV if unacceptably light anaesthesia persisted at this point.

The oxygen flowmeter was decreased to a flow equal to 20ml.kg^{-1}.min^{-1} ten minutes after successful intubation, with a minimum flow of 1.0 l.min^{-1} oxygen being used. Although this minimum value resulted in oxygen flow well above standard flow rates for rebreathing circuits for smaller dogs, this minimum value was raised on the basis that the capnograph and end-tidal anaesthetic monitor continuously withdrew at least 500ml.min^{-1} gas from the circuit (*Section 2.5.3.1.2*).

Any dog which remained apnoeic for a period of greater than 30sec was ventilated by hand at a rate of 4breaths.min^{-1}. A positive pressure of 10cmH_2O was the target during these artificial breaths.

From this point, the vaporiser output was adjusted based on standard criteria for the depth of anaesthesia, as discussed below (*Section 2.3.4*). The animal was then instrumented as discussed below, and prepared for surgery.

2.3.3.2 Intravenous agent inductions

Cases enrolled into an intravenous induction group were given propofol[30] for induction of general anaesthesia. A volume equalling 6mg.ml^{-1} was drawn up into an appropriately sized syringe[31] with needle[32]. As with inhalant inductions, dogs in excess of 20kg bodyweight were induced on the floor, those less than this weight were induced on a table where they would remain until being moved to the surgery table. All dogs were initially held by a veterinary nurse, with an additional person used to hold the hindquarters of larger dogs only when necessary. The objective was to use a minimal dose of propofol which would allow endotracheal intubation of the animal without overt signs of resentment. Such signs would include gagging, coughing, chewing or vigorous head movement.

After confirming patency and proper placement of the intravenous catheter with a bolus of heparinized saline, a bolus of 2mg.ml^{-1} propofol was injected. The

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[30] Propofol Injection. Abbott Australasia, Kurnell, NSW, Australia

[31] 3ml, 5ml, 10ml, 20ml syringe: Terumo Syringe, Terumo (Phillipines) Corporation, Phillipines

[32] 22Gx1.00" Terumo Needle, Terumo Corporation, Tokyo, Japan

stopwatch was started at the commencement of this injection. Propofol was injected rapidly, at approximately 1ml.sec^{-1}, and was followed by 1.0ml of heparinized saline to flush the intravenous catheter clear of propofol.

Following this bolus, the patient was observed. Preparedness for endotracheal intubation was based on respiratory rate and quality, eye position, muscle tone and response to opening of the mouth. The initial bolus was given a maximum of 45sec to reach peak effect.

A further bolus of 1mg.kg^{-1} was delivered as above if the effect of the initial injection were considered insufficient, and the results observed. Further doses of 1mg.kg^{-1} were delivered in this manner at 45sec intervals until the animal was adjudged ready for intubation.

Endotracheal intubation was performed as for inhalant inductions. Following successful intubation the patient was connected to the anaesthetic machine and the tube cuff inflated. Patients induced and intubated on the floor were moved onto the table prior to connection. As with dogs induced with an inhalant agent, those less than 10kg bodyweight breathed through a paediatric rebreathing circuit, those heavier through a co-axial rebreathing circuit. The anaesthetic machine was set up as described for inhalant inductions. No inhalant agent entered the circuit prior to connection to the intubated animal.

Upon connection, the oxygen flow into the circuit was set to 3.0 l.min^{-1}. The inhalant agent vaporiser output was then set to an initial value of 2.0% for halothane, 3.0% for isoflurane, and 4.5% for sevoflurane. This output was maintained for 5 minutes. These delivered doses for isoflurane and sevoflurane equated to twice previously published MAC doses, rounded to the nearest 0.5%. The slightly higher dose of halothane compared to that used in the inhalant agent groups at this point was used to shorten the onset of halothane anaesthesia, due to the ultra-short action of propofol.

From this point on, animals in the intravenous induction groups were treated identically to those in inhalant induction groups. A single exception was the treatment of animals becoming unacceptably light under anaesthesia soon after intubation. Patients demonstrating gross purposeful movements, swallowing or chewing on the endotracheal tube within twenty minutes from commencement of induction were given a further dose of propofol to improve the transfer of anaesthesia from the intravenous induction to the inhalant maintenance agent. This was achieved with an

initial bolus of 1mg.kg^{-1} propofol intravenously. Further 1mg.kg^{-1} boluses were to be given at 45sec intervals until signs of unacceptably light anaesthesia were abolished.

As with those in inhalant induction protocols, the dog was then moved into lateral recumbency, instrumented as discussed below, and prepared for surgery. The oxygen flow rate was decreased to 20ml.kg^{-1}.min^{-1} ten minutes after successful intubation, with a minimum flow rate of 1.0 l.min^{-1}, as described for inhalant inductions.

2.3.4 Maintenance of anaesthesia

Anaesthesia was maintained throughout the surgery using only the selected inhalant agent in oxygen. Adjustment of vaporiser output was controlled by the veterinarian in charge of the anaesthetic (the author). The decision to increase or decrease the concentration of inhaled anaesthetic agent was made based on standard criteria for assessing depth of anaesthesia. These included heart rate, respiratory rate and pattern, pulse quality, mucous membrane colour, palpebral reflex, jaw tone and response to movement and surgical stimulation. The goal was to achieve a level of anaesthesia just sufficient to allow the desexing surgery to be undertaken without evidence of conscious response, subconscious movement or excessive sympathetic nervous system tone from the patient.

Instrumentation, clipping of hair and preparation for surgery were undertaken on the induction table, before movement of the patient to the surgical table. Movement required disconnection of the circuit for approximately 10sec.

No attempt was made to reduce the concentration of inhaled anaesthetic agent close to the completion of surgery. The vaporiser output was maintained at the same output as had been selected by that time.

Intravenous fluid therapy was administered to all animals. A crystalloid replacement fluid[33] was infused at the rate of 10ml.kg^{-1}.hr^{-1}, using the intravenous catheter placed prior to induction. Administration was commenced as soon as possible after induction and ceased at the end of surgery. Gravity feed giving sets were used, an adult set[34] (20drops.ml^{-1}) for dogs in excess of 9kg bodyweight, and a paediatric

[33] Plasma-Lyte 148 Rep. Baxter Healthcare, Old Toongabbie, NSW, Australia

[34] Solution Administration Set (20drops/ml). Baxter Healthcare Pte Ltd, Singapore

system (60drops.ml^{-1}) with burette[35] for those less than 9kg. Body temperature was conserved via the use of an electric heat pad[36] on both the induction and surgery tables, warm water bottles in the form of 0.5 and 1.0litre intravenous fluid bags converted for the purpose, and blankets. A bland ophthalmic ointment[37] was administered to the eyes.

Each patient received 0.2mg.kg^{-1} meloxicam[38], intravenously soon after first surgical incision. Each dog also received routine vaccination[39] and antibiotics[40] prior to first surgical incision. The antibiotics and vaccination were not considered to have any influence over the nature of the anaesthetic or the recovery period.

2.3.5 Recovery

At the completion of surgery, defined as cutting of the last skin suture, the vaporiser setting was switched to "Off", and the oxygen fresh gas flow set to 3.0 l.min^{-1}. The rebreathing bag was evacuated once into the gas scavenge line. The dog was positioned in lateral recumbency. The only additional stimulation the dog received for the next ten minutes was cleaning of the surgical site with saline soaked gauze[41], and the removal of the arterial catheter and oesophageal temperature probe (*Sections 2.5.3.1.1, 2.5.3.1.3*).

The dog remained connected to the anaesthetic machine circuit for ten minutes following end of surgery unless it was adjudged ready for extubation within that time. After ten minutes, or immediately following extubation if performed within that period, the dog was disconnected from the circuit and moved to the recovery area. The animals were placed on a blanket on the floor, with a heat lamp stationed approximately 1m away. They were supervised to ensure they inflicted no harm to themselves during this period.

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[35] Dosifix (60drops/ml). Braun Melsungen AG, Germany

[36] ICU Patient Warming Pad. Easy Veterinary Equipment, Seven Hills, NSW, Australia

[37] Lacri-Lube. Allergan Australia, Sydney, Australia

[38] Metacam. Boehringer Ingelheim Pty Ltd, Vetmedica Division, North Ryde, NSW, Australia

[39] Canvac C4+BB. CSL Limited, Parkville, Victoria, Australia

[40] Clavulox (Injection)(amoxicillin-clavulanic acid) 20mg/kg SC. Pfizer Animal Health, West Ryde, NSW

[41] Gauze Swabs. Smith & Nephew Pty Ltd, Clayton, Victoria, Australia

Dogs were considered ready for extubation when they fulfilled one of the following criteria: conscious chewing on the endotracheal tube, conscious swallowing, or lifting the head. An increase in respiratory rate, change in respiratory pattern or blinking was not considered sufficient for extubation.

Following extubation, dogs were not further handled until after they had stood, unless they required manual restraint or support to avoid injuring themselves during recovery.

The point at which the animal stood was the last piece of data to be collected, and care of the dog following this time was as per routine for the CDC, with three postoperative examinations over the following 18-24hr, before the dogs were discharged from the clinic.

2.3.5.1 Supplementary analgesia

During recovery, dogs were observed for quality of recovery. Any dog showing marked signs of pain was given supplementary analgesia in the form of an intramuscular injection of 0.4mg.kg^{-1} morphine. Such cases were given the lowest score for recovery quality (*Section 2.5.4.2.1*).

2.4 Surgery

Dogs were desexed using routine surgical techniques. Ovariohysterectomy was performed via a ventral midline approach with the dog positioned in dorsal recumbency. Ovarian ligaments were ruptured by hand and the pedicles ligated using absorbable suture material[42]. The uterus was ligated with absorbable suture and transected just cranial to the cervix. Three layer closure of the abdomen was performed with continuous suture patterns in the linea alba and subcutaneous layers, and cruciate sutures of nonabsorbable suture material[43] in the skin.

Male dogs were castrated through a prescrotal incision with the patient positioned in dorsal recumbency. Both open and closed techniques were used. Two or

[42] PDS II. Ethicon, Inc., Somerville, NJ, USA

[43] Ethilon. Ethicon, Inc., Somerville, NJ, USA

three layer closures were undertaken, with an optional continuous layer in the scrotal tunic, followed by a continuous subcutaneous layer and nonabsorbable cruciate sutures in the skin.

Each surgery was performed by two final year veterinary science students from the University of Sydney, under the direct supervision of a veterinarian. No other surgical procedures were undertaken.

2.5 Data Collection

2.5.1 Prior to anaesthesia

2.5.1.1 Quantitative data

2.5.1.1.1 General health status

Data collection prior to induction of general anaesthesia consisted of a routine clinical pre-anaesthesia examination, including auscultation of the heart and lungs, palpation of the peripheral pulse, assessment of mucous membrane colour and capillary refill time, rectal temperature, abdominal palpation and general demeanour. Percutaneous venipuncture of a jugular vein was performed, with 1.0ml of blood placed in an evacuated tube containing CaEDTA as an anticoagulant, and 1.0ml in an uncoated evacuated tube. This sample provided a preanaesthetic baseline for any patient that had intra- or post-operative complications.

2.5.1.2 Qualitative data

All qualitative assessments were made by the author.

2.5.1.2.1 Demeanour

Each dog was assessed as to its overall demeanour, based on response to initial handling for physical examination and jugular venipuncture. This assessment was marked in the form of a number between 0 and 4 inclusive, as follows:

Score 0: *Abnormal, signs of depression (would be excluded from study)*

Score 1: *Anxious and aggressive, difficult to handle, requiring continual firm restraint, including muzzle.*

Score 2: *Anxious, frightened, requires generally firm restraint, but not aggressive.*

Score 3: *Nervous and/or excitable, requires less restraint.*

Score 4: *Calm, friendly, easy to handle, minimal restraint required.*

This data was used as part of the active selection of dogs into premedication or no-premedication groups, as described above (*Section 2.2*).

2.5.1.2.2 Sedation

Dogs that were premedicated were scored just prior to induction of general anaesthesia as to their sedation and resistance to handling. Specifically:

Score 3: *Sedation profound – resistance none: Dog is recumbent, can be aroused but not willing to stand and walk. No resistance to being moved or manipulated. Seems barely aware of being manipulated.*

Score 2: *Sedation moderate – slight resistance: Dog recumbent when not aroused. Will stand and walk if encouraged. Possibly some resistance when manipulated and moved however only one person required to move and restrain dog.*

Score 1: *Sedation slight – resistance moderate: Dog obviously more relaxed and calm compared to prior to premedication. Walks easily, not necessarily recumbent when not being aroused. May require two people to manipulate and restrain dog.*

Score 0: *Sedation none – resistance profound: Dog is excitable, unchanged from prior to premedication. Marked force may be required for moving and manipulating the patient.*

2.5.2 During induction of general anaesthesia

2.5.2.1 Quantitative data

During the induction process, qualitative and quantitative measurements were undertaken. A person not involved in restraining or medicating the animal recorded the relevant data on the data collection sheet. This person also controlled the stopwatch.

The time of commencement was set as the time when the induction mask was first placed over the dog's muzzle to commence preoxygenation, for inhalant induction, or, for intravenous inductions, the point at which injection of propofol was started. The stopwatch was started at this point, with this device then counting upwards from zero in hours, minutes and seconds. The stopwatch was not stopped from this point until the end of data recording postoperatively. All times were recorded to a resolution of 1sec as they appeared on the stopwatch.

The following quantitative data was collected during the induction process.

2.5.2.1.2 Time to intubation

The time at which the laryngoscope was removed from the mouth immediately following successful endotracheal intubation of the patient.

2.5.2.1.3 Intubation attempts

An unsuccessful attempt to intubate an animal, which required an additional dose or doses of the induction agent to be given before intubation could again be attempted, was considered a failed attempt. Incorrect endotracheal tube size selection requiring a change of tube prior to successful intubation was not considered a failed attempt if no further induction agent was required before successful intubation was achieved. The number of failed attempts, plus one successful attempt, was the total recorded.

2.5.2.1.4 Dose of propofol prior to intubation

The total dose of propofol, in milligrams, administered prior to successful endotracheal intubation for patients undergoing intravenous agent induction.

2.5.2.1.5 Dose of propofol post-intubation

Any further dose of propofol given soon after successful endotracheal intubation. Such a dose would be delivered to maintain a minimum acceptable level of anaesthesia during the period whilst the selected inhalant agent was achieving an appropriate anaesthetic concentration within the patient (*Section 2.3.3.1, 2.3.3.2*).

2.5.2.2 Qualitative data

2.5.2.2.1 Tolerance of mask

Patients induced with an inhalant agent were scored for tolerance of mask. This represented the response of the dog to the induction mask in the period of preoxygenation, and did not include any response noted after inhalant anaesthetic entered the breathing circuit. It was scored on the following scale:

Score 4.<u>*Excellent*</u>*: No attempts made to remove head from mask. Minimal restraint required to hold dog in position – one nurse sufficient. Respiratory rate and pattern close to normal within 30sec of mask placement.*

Score 3. <u>*Good*</u>*: No more than two attempts to withdraw head from mask, mask easily replaced after withdrawal. Minimal restraint required – one nurse sufficient. Respiratory rate and pattern possibly disrupted from normal throughout preoxygenation.*

Score 2. <u>*Fair*</u>*: More than two attempts to withdraw head from mask, may be difficult to replace mask after withdrawal. Greater level of restraint required – additional person may be required for larger dogs, firm "scruffing" required. Respiratory rate and pattern disrupted throughout preoxygenation.*

Score 1. <u>*Poor*</u>*: More than two attempts to withdraw head from mask, reapplication of mask difficult. Withdrawal attempts include use of limbs to remove mask. Greater level of restraint required. Respiratory rate and pattern disrupted throughout preoxygenation. Dog visibly distressed by mask.*

Score 0. *Unacceptable: Unable to keep mask in place and/or restrain dog in position. Dog obviously distressed and/or aggressive. Mask induction abandoned – move to intravenous induction.*

2.5.2.2.2 Quality of induction

This variable represented the nature of the entire induction process to the point of successful endotracheal intubation. It was scored on the following scale:

Score 4. *Excellent: Smooth and rapid transition from conscious to anaesthetised with minimal resistance in terms of movement. Minimal restraint required – one nurse sufficient. Muscle relaxation sufficient for easy opening of mouth by nurse for endotracheal intubation.*

Score 3. *Good: Transition from conscious to anaesthetised associated with some movements requiring restraint by a single assistant. Movements do not interfere with process of endotracheal intubation, muscle relaxation sufficient for easy opening of mouth.*

Score 2. *Fair: Moderate excitation present during transition from conscious to anaesthetised, in terms of gross movement, vocalisation, urination or defecation. Firm restraint required – an additional person required for larger dogs. Poor to medium muscle relaxation, making opening mouth for endotracheal intubation more difficult.*

Score 1. *Poor: Marked excitation, in terms of gross movement and struggling, vocalisation, urination or defecation. Firm restraint required but still difficult to retain dog in position. Poor muscle relaxation making opening mouth difficult. Dog shows signs of distress.*

Score 0. *Unacceptable: Marked excitation and struggling, and/or aggression. Unable to maintain dog in position despite firm restraint. Dog shows obvious signs of distress. Inhalant induction protocols – abandon, move to intravenous induction. Intravenous induction protocols – abandon, reassess suitability of dog for anaesthesia at this time.*

2.5.2.2.3 Quality of transfer

A measure of the adequacy of anaesthesia in the first twenty minutes following successful endotracheal intubation – the period of transfer between the induction agent and the maintenance agent. Scored on the following scale:

Score 4. *Excellent: Patient remains well anaesthetised throughout the period. Respiratory rate and pattern is within normal ranges for an anaesthetised dog, initial apnoea lasts no longer than 30sec. Palpebral reflex may or may not be present, jaw tone medium to slack. No conscious or unconscious movement. Dog may be moved from lateral to dorsal recumbency without evident lightening of anaesthesia.*

Score 3. *Good: Patient remains well anaesthetised. Respiratory rate and pattern may be somewhat irregular – either apnoea prolonged more than 30sec, or more vigorous "panting" type breathing. No conscious or unconscious movements whilst dog's position is unchanged, mild unconscious movements may be observed when position is changed.*

Score 2. *Fair: Patient becomes notably lighter under anaesthesia during the period. Respiratory pattern and rate are irregular. Some conscious or unconscious movements occur when patient position remains unchanged. Conscious swallowing or chewing on endotracheal tube occurs. Palpebral reflex present for most of the period, jaw tone at some stage tight. For patients in intravenous induction protocols, a single further dose of propofol is required to avoid an unacceptable lightening of anaesthesia.*

Score 1. *Poor: Patient becomes notably lighter under anaesthesia. Respiratory rate and pattern irregular. Conscious movements occur, chewing or conscious swallowing on endotracheal tube occurs. Restraint may be necessary to avoid patient injuring self or staff. For patients in intravenous induction protocols, one or more additional doses of propofol are required.*

2.5.3 During maintenance of anaesthesia

2.5.3.1 Quantitative data

2.5.3.1.1 Cardiovascular variables

Heart rate (HR), peripheral arterial haemoglobin saturation (SpO_2), systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and mean arterial pressure (MAP) were monitored throughout anaesthesia.

As soon as feasible following the induction of anaesthesia, a transmission pulse oximeter probe was placed on a portion of the tongue at least 5mm in thickness to measure SpO_2. This was expressed as a percentage. The electronic monitor[44] which displayed a plethysmogram representation of SpO_2, blood pressure and temperature data, provided no means for calibration of the pulse oximeter. A single probe was used for all dogs.

Blood pressures were measured directly. An over-the-needle catheter[45], either 22Gx1.00", or 20Gx1.16", was placed into the dorsal metatarsal artery. If attempts to place this catheter were unsuccessful by 30minutes after induction, blood pressure

[44] Dinamap Plus. Critikon, Tampa, FL, USA.

[45] BD Insyte. Becton-Dickinson Medical (S) Pte Ltd. Singapore.

measurement was abandoned. Such cases were, however, not excluded from the study. Connected to this intra-arterial catheter was a short T extension set[46], and two 150cm minimum volume extension sets[47] designed for blood pressure measurement separated by a three way stopcock[48]. The distal end of this apparatus was then connected to the blood pressure transducer[49], a quartz crystal transducer which produced a continuous waveform on the electronic monitor. This transducer kit included a continuous flush mechanism, which allowed a steady low flow of heparinised saline through the arterial line to prevent clotting. Arterial blood pressures were measured in millimetres of mercury. The transducer was zeroed to atmospheric pressure prior to the commencement of data collection in each case. A single transducer was used for all dogs.

Heart rate was generated by the electronic monitor from pulse oximeter data until the blood pressure transducer was operational. This value was cross checked by manual pulse palpation or cardiac auscultation if the pulse oximeter waveform was not consistent with clear pulse detection. An SpO_2 reading was not recorded in such instances.

2.5.3.1.2 Respiratory variables

Respiratory variables measured throughout anaesthesia were respiratory rate, end-tidal carbon dioxide, and inspiratory and end-tidal expiratory inhalant anaesthetic concentrations.

End-tidal partial pressure of carbon dioxide and respiratory rate were measured by capnograph[50]. Inspiratory and end-tidal expiratory concentrations of inhalant anaesthetic were measured by a separate gas analyser[51]. End-tidal carbon dioxide was recorded in millimetres of mercury. Inhalant agent concentrations were measured in volumes per cent. An adaptor placed between endotracheal tube and

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[46] Abbott Lifeshield Microbore Extension Set. Abbott Laboratories, North Chicago, IL, USA.

[47] Extension Tubing DCO150HP. Dispo-Med, Malaysia.

[48] ThreeWay Stopcock. Baxter Healthcare Corporation, Deerfield, IL, USA.

[49] Monitoring Kit, Transpac IV. Abbott Critical Care Systems, Sligo, Ireland.

[50] Ohmeda 4700 OxiCap Monitor. Ohmeda, Louisville, CO, USA.

[51] Ohmeda 5330. Ohmeda, Louisville, CO. USA.

breathing circuit provided a port for continuous gas sampling, at a rate of 250ml.min^{-1} minimum for the end-tidal anaesthetic monitor, and 250ml.min^{-1} for the capnograph. This adaptor was placed on the breathing circuit prior to induction, and per the operating manuals, both machines were switched on at least 30minutes prior to induction to allow readings to stabilise. Calibration was undertaken as recommended by the manufacturer of both machines, using gases of known concentration. Calibration was undertaken weekly for the capnograph, and monthly for the end-tidal anaesthetic monitor. Monthly adjustment of barometric pressure for the end-tidal anaesthetic monitor was addressed, using a mercury column barometer as reference. During anaesthesia, respiratory rate was cross-checked by visual measurement of rebreathing bag movement over a 30sec period.

2.5.3.1.3 Temperature

An oesophageal temperature probe was placed soon after induction. It was advanced to a point approximately equivalent to the thoracic inlet. This probe was connected to the same monitor as provided the blood pressure and SpO_2 data, with readings in degrees Celsius to a resolution of 0.1°C. The monitor provided no means for calibration of this probe, however its readings were compared to reference values in a water bath containing a calibrated thermometer. The same probe was used for all cases.

2.5.3.1.4 Frequency of data collection

During maintenance of anaesthesia, the above variables were recorded every five minutes for the first hour, then every ten minutes. These intervals were measured from commencement of induction. A first reading was taken as soon as the pulse oximeter, capnograph, end-tidal anaesthetic monitor and temperature probe were attached, with readings then taken at the five minute intervals from induction.

2.5.3.1.5 Other quantitative data

During the maintenance phase of anaesthesia, two other data points were recorded. Time of incision represented the time at which the initial surgical incision

was made. End of procedure time was the conclusion of surgery, defined as the completion of the last skin suture. As mentioned previously, this was also the time at which the inhalant anaesthetic vaporiser was switched off. These times were recorded to a resolution of 1 second, timed from commencement of induction.

2.5.3.2 Qualitative data

No qualitative data was recorded during the maintenance phase of anaesthesia.

2.5.4 Recovery from anaesthesia

2.5.4.1 Quantitative data

2.5.4.1.1 Time of extubation

The time the endotracheal tube was removed, following the protocol outlined above (*Section 2.3.5*).

2.5.4.1.2 Time to righting

Following extubation, the time at which the dog first moved itself into sternal recumbency and was able to maintain such a position. Momentary head raising was not considered righting.

2.5.4.1.3 Time to standing

The time the dog first raised itself to a standing position.

2.5.4.2 Qualitative data

2.5.4.2.1 Quality of recovery

The final piece of data to be considered was the quality of recovery. This encompassed the period from the discontinuation of inhalant anaesthesia to any responses demonstrated at or soon after the patient stood after anaesthesia. It was scored on the following scale:

Score 4. *Excellent: Smooth transition from anaesthesia to full consciousness. No paddling, tremors or other unconscious movements. No vocalising. Salivation normal, not excessive. Transfers from lateral recumbency to sternal with one or two attempts. No obvious signs of pain.*

Score 3. *Good: Mostly smooth transition from anaesthesia to full consciousness. Some mild unconscious movements may be seen. No vocalising. Salivation may be increased, some general signs of pain may be witnessed. More than two attempts may be necessary for transition from lateral to sternal recumbency.*

Score 2. *Fair: Transition from anaesthesia to full consciousness is not smooth. Moderate paddling or other unconscious movements, persist well into recovery period. Vocalisation present. Patient has difficulty positioning itself, may thrash about for short periods. Manual restraint may be required for short periods. Hypersalivation possibly present. Moderate to marked signs of pain.*

Score 1. *Poor: Rough transition from anaesthesia to full consciousness. Regular unconscious movements persist well into consciousness, thrashing for sustained periods. Animal will injure itself without manual restraint, may respond aggressively to restraint. Marked signs of pain. Hypersalivation. Sustained vocalisation.*

2.6 Statistical Analysis

All analyses excepting the induction dose of propofol (*Section 2.6.3*) were performed using the computer program SPSS[52]. Propofol dose analysis was performed using the computer program Minitab[53].

*2.*6.1 Time to intubation

All times were converted to seconds for analysis. A two-way analysis of variance (ANOVA) was undertaken to analyse times to intubation, with premedication and induction agent as the independent variables. Interaction between induction agent and premedication was investigated. Where *F* values were significant, post-hoc tests of Least Significant Difference were used.

[52] SPSS 11.5. SPSS Inc, Chicago, Illinois, USA

[53] Minitab 13.32. Minitab Inc, State College, Philadelphia, USA.

2.6.2 Quality of induction

Scores for quality of induction were collapsed into a two-level variable. All scores less than 4 (excellent) were reclassed as category 1. All scores of 4 (excellent) were reclassed as category 2. Logistic regression was then performed on this new variable. A Hosmer-Lemeshow test was performed to confirm goodness of fit to the model, and residuals were inspected.

2.6.3 Propofol dose for induction

Doses were converted to $mg.kg^{-1}$ using the weights recorded prior to anaesthesia. A two sample T-test was performed on this data. Because of the heteroscedasticity of the two groups, this data was also analysed using a Mann-Whitney U test. The data was also transformed by natural log to improve normality of the distribution, and a two sample T-test performed on the transformed data.

2.6.4 Time to righting

A natural log transformation was undertaken to normalise the data. A two-way ANOVA was performed, with premedication, induction agent, procedure time and temperature at procedure end as the independent variables. Interaction between these variables was investigated. Where *F* values were significant, post hoc tests of Least Significant Difference were used.

2.6.5 Time to standing

This data was analysed using a similar model as time to righting (Section 2.6.4).

2.7 Costing of agents

The costs involved in undertaking inhalant induction with the three inhalant agents was calculated, based on the method described in Steffey (1996) for determination of the volume of liquid volatile agent consumed. The following

assumptions were used. The mean time to intubation for all cases induced with each agent was used, with oxygen flow rates and vaporiser settings as described above (*Section 2.3.3.1*). Physical data for the agents was as summarised in Table 1.1. Ambient temperature was assumed to be 20°C.

The cost involved in induction with propofol was also calculated. The mean dose for cases induced with and without premedication was used.

The cost involved in maintaining anaesthesia in a patient using each of the three inhalant agents was calculated, assuming a vaporiser setting of 1.5.MAC based on the upper limit of MAC values expressed in Table 1.2, at a total fresh gas flow of 1.0 $l.min^{-1}$. The method described in Steffey (1996) was again used for determination of liquid anaesthetic agent used.

Costs for each agent were obtained from a veterinary wholesaler[54], and represent the GST-inclusive price to the University Veterinary Centre, Camden, in August, 2004. One 250ml bottle of halothane, isoflurane or sevoflurane cost A$43.08, A$166.25, and A$462.00 respectively. One 20ml (200mg) vial of propofol cost A$14.95. Vaporiser costs were obtained from a veterinary equipment dealer[55] in August 2004.

[54] Lyppard (NSW). Castle Hill, NSW, Australia.

[55] Austvet. Vermont, Victoria, Australia.

Chapter 3: Results

3.1 Cases enrolled

Seventy-one dogs were enrolled into the study during the data collection period. This represents those considered healthy on the basis of physical examination prior to anaesthesia and within the nominated age range (*Section 2.2*). Forty-four of these dogs were males scheduled for castration and 27 were females to undergo ovariohysterectomy. One male was cryptorchid.

The dogs weighed an average 14.2 ± 11.2kg (mean ± SD, range 2.0 to 46.0kg).

3.2 Group allocation

According to the assessment of demeanour described above (*Section 2.5.1.2.1*), a total of 24 dogs were given a score of either 3 or 4, and were placed into groups involving no premedication. The remaining 47 dogs were given scores of 1 or 2, placing them into groups including premedication. The numbers allocated into the various groups is detailed in the table below (*Table 3.1*). The data from one dog in the sevoflurane induction after premedication group was discarded (*Section 3.4.1*), leaving thus a total of 8 dogs in this group.

Maintenance agent ▶	**Halothane**		**Isoflurane**		**Sevoflurane**	
	NP	**P**	**NP**	**P**	**NP**	**P**
Intravenous induction	4	8	4	8	4	7
Inhalant induction	4	7	4	8	4	9*

Table 3.1 Experimental group allocation.
NP = No Premedication.
P =Premedication.
* Data from one dog discarded.

3.3 Prior to induction of anaesthesia

Venipuncture was possible on all but four dogs without premedication. As part of the assessment of demeanour, these four exceptions were all placed into groups including premedication.

Intravenous catheterisation of the left or right cephalic vein was successfully undertaken on all cases prior to induction of anaesthesia. In all cases, these catheters remained patent throughout the period of anaesthesia, and intravenous fluids were delivered as outlined above (*Section 2.3.4*).

3.4 Induction of anaesthesia

3.4.1 Inhalant inductions

Of the 37 cases in inhalant induction groups, 35 were induced using the nominated agent. One dog in the (No premedication + Isoflurane) group and one in the (No premedication + Sevoflurane) group were induced with propofol following marked resistance to mask induction fulfilling the criteria of Section 2.3.3.1 for abandoning inhalant induction by mask. It should be noted that these two cases were excluded from the statistical analysis of induction time (*Section 3.4.4*).

The first of these two dogs was a 15kg female young adult Blue Cattle Dog presented to the CDC for ovariohysterectomy. It was given a score of 3 for its demeanour (*Section 2.5.1.2.1*), and a score of 2 for tolerance of mask (*Section 2.5.2.2.1*). It accepted the introduction of isoflurane to the circuit for 3min35sec before vigorously removing its head from the mask and requiring marked restraint to prevent its escape. Mask induction was abandoned and anaesthesia successfully induced with 90mg of propofol ($6mg.kg^{-1}$) IV.

The second dog was a 29kg male adult Golden Retriever. It was given a score of 3 for its demeanour and 3 for tolerance of mask. This dog cooperated with sevoflurane in the circuit for 1min45sec before responding in a similar fashion to the previously discussed case. Mask induction was abandoned and anaesthesia was induced with 175mg of propofol ($6mg.kg^{-1}$) IV.

One male dog induced with sevoflurane after premedication was found to have an infected wound with abscessation. This dog was not desexed, and thus the data from this case was discarded.

3.4.2 Intravenous inductions

All 35 cases in intravenous induction groups were successfully induced using propofol according to the protocol in Section 2.3.3.2.

One dog withdrew and shook the catheterised foreleg upon administration of propofol, signs compatible with irritation from the administered drug. These signs were transitory, resolving in less than 10sec. The dog was in a group not receiving premedication. No other dog showed similar signs.

None of the 35 dogs showed the twitching or tonic-clonic type movements previously associated with propofol (*Section 1.2.5.3*).

3.4.2.1 Propofol dose requirements

Dogs induced with propofol after no premedication required significantly more propofol for intubation than those induced with propofol after premedication ($4.32 \pm 0.61 mg.kg^{-1}$ (mean ± SE) vs $2.68 \pm 0.24 mg.kg^{-1}$; $p = 0.0095$ (two sample T test, untransformed data), $p = 0.0074$ (two sample T-test, transformed data), and $p<0.01$ (Mann-Whitney U test)).

3.4.3 Intubation attempts

Fifty-nine of 71 dogs were intubated on the first attempt. Ten dogs required 2 attempts, the remaining two requiring three attempts. The initial attempt failed in only one dog due to incorrect endotracheal tube size selection.

There was no association between experimental group and requirement for greater than one intubation attempt.

3.4.4 Time to intubation

The time to endotracheal intubation in dogs anaesthetised with isoflurane by mask was significantly shorter than for those anaesthetised with halothane by mask (172.4 ± 15.0 vs 221.4 ± 14.0sec, p=0.021)(*Table 3.2*).

There was no significant difference in time to intubation between dogs anaesthetised with sevoflurane by mask and those anaesthetised with halothane by mask (196.2 ± 14.8 vs 221.4 ± 15.0sec, p=0.207). Similarly, there was no significant difference in time to intubation between dogs anaesthetised with isoflurane by mask and those anaesthetised with sevoflurane by mask (196.2 ± 14.8 vs 172.4 ± 15.0sec, p=0.267).

The time to endotracheal intubation in dogs anaesthetised with propofol by injection (85.4 ± 7.7sec) was significantly shorter than for those anaesthetised with halothane (221.4 ± 14.0sec), isoflurane (172.4 ± 15.0sec) or sevoflurane (196.2 ± 7.7sec, p<0.001 in each case)(*Figure 3.1*).

Dogs induced with propofol after premedication had a significantly shorter time to intubation than those induced with propofol without premedication (59.5 ± 9.4 vs 111.4 ± 12.6sec, p=0.002). In dogs induced with a gaseous agent, there was no significant difference in time to intubation between those not given premedication and those given premedication (halothane 225.6 ± 21.8 vs 217.2 ± 16.8sec, p= 0.757; isoflurane 176.8 ± 25.0 vs 168.1sec, p= 0.770; sevoflurane 222.6 ± 25.6 vs 169.7 ± 14.4sec, p= 0.075).

	All Cases		*No Premedication*		*Premedication*	
	Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Halothane	221.4*	14.0	225.6	21.8	217.2	16.8
Isoflurane	172.4*,¶	15.0	176.8	25.0	168.1	16.3
Sevoflurane	196.2*	14.8	222.6	25.6	169.7	14.4
Propofol	85.4¶	7.7	111.4	12.6	59.5	9.4

Table 3.2 Time to intubation (sec)
* Significantly different from propofol ($p<0.05$).
¶ Significantly different from halothane ($p<0.05$).

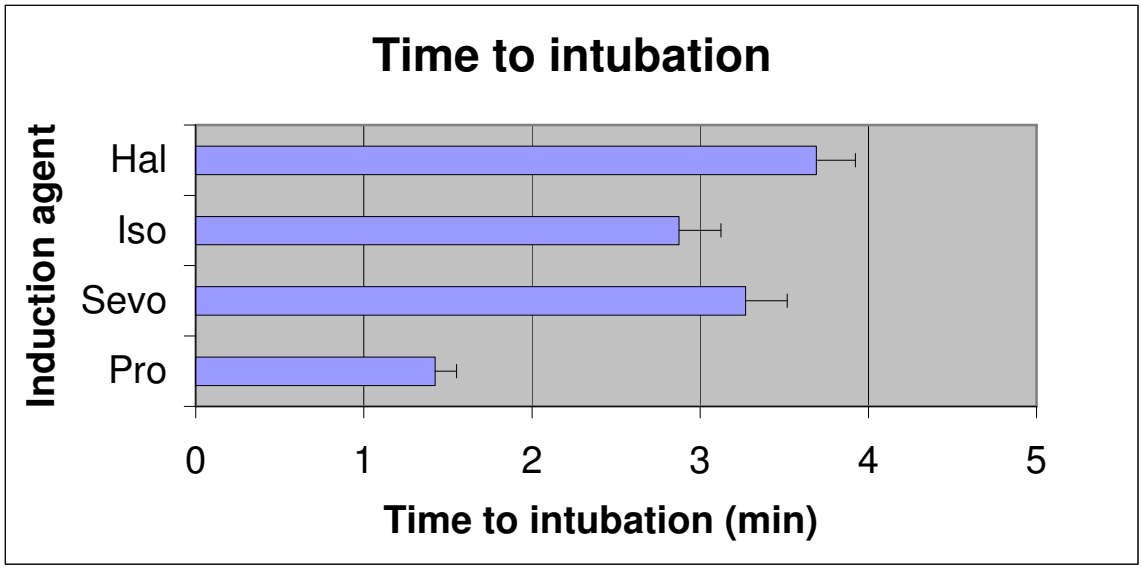

Figure 3.1: Time to intubation, in minutes
Hal: Halothane
Iso: Isoflurane
Sevo: Sevoflurane
Pro: Propofol

3.4.5 Quality of induction

An outline of quality of induction scores is shown in Table 3.3. A clear majority of all inductions (54 of 71) were scored as either of good or excellent quality. Data from the dog with abscessated wound was not considered. Due to operator error, two other cases were not given quality of induction scores.

Dogs receiving premedication were 11.7 times more likely to be given an induction quality score of 4 than those not premedicated (OR 11.7, 95% CI: 2.7 – 50.3).

Dogs receiving propofol for induction were 4.4 times more likely to be given an induction quality score of 4 than those induced with a gaseous agent by mask (OR 4.4, 95% CI: 1.3 – 14.2).

In dogs that resisted the process of inhalant induction, it was commonly noted that signs of resistance commenced between 45 and 55sec after the inhalant entered the breathing circuit.

Quality of induction	*Number of cases*
0 - Unacceptable	2
1 – Poor	5
2 – Fair	7
3 – Good	24
4 – Excellent	30

Table 3.3 Quality of induction scores

3.5 Intraoperative Variables

A summary of the results for the measurement of mean arterial blood pressure, heart rate, end-tidal carbon dioxide and end-tidal anaesthetic concentrations is shown

in Table 3.4, broken down by gaseous anaesthetic agent and presence of premedication.

The single mean value given for each of these variables in Table 3.4 was produced by pooling all measurements between 20min and 90min inclusive after commencement of induction. Specifically, readings from 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80 and 90min after induction were included for each variable.

This single mean value was considered an acceptable representative for three reasons. By 20min after induction, the cardiorespiratory effects of propofol when used for induction should be effectively dissipated (Brussel *et al.* 1989; Ilkiw *et al.* 1992), avoiding any potential confounding effect. Secondly, the period 20min to 90min after commencement of induction represents the period with a appropriate quantity of data recordings. As can be seen in Figures 3.2 – 3.6, after 90min, some groups have two or less measurements, decreasing the validity of the data. In addition, particularly for measurement of mean arterial pressure, fewer readings were taken prior to 20min due to the time involved with placement of the intraarterial catheter. Thirdly, again referring to Figures 3.2 – 3.6 of the variables measured intraoperatively, the mean measurements between 20min and 90min remained relatively stable amongst most groups, making a single value a reasonable representation of the period.

Based on these mean values, the decrease in required dose of inhalant between dogs not given premedication and those given premedication was 28.1% for halothane, 21.7% for isoflurane, and 1.8% for sevoflurane.

	All cases		*No premedication*		*Premedication*	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
HR (beats.min^{-1})						
Hal	97.7	19.0	102.7	12.1	95.0	21.4
Iso	106.7	16.1	111.4	17.4	104.0	14.7
Sevo	103.9	21.1	101.9	17.6	105.2	23.0
MAP (mmHg)						
Hal	78.6	16.3	75	14.1	81.1	17.3
Iso	77.3	14.5	76.3	13.8	77.9	15.0
Sevo	81.1	18.4	85.9	18.5	77.8	17.7
$ETCO_2$ (mmHg)						
Hal	42.9	7.0	44.0	8.5	42.2	5.8
Iso	46.1	5.9	47.3	7.1	45.3	5.0
Sevo	44.3	7.4	45.4	7.3	43.6	7.5
ETAgent (vol%)						
Hal	1.11	0.35	1.36	0.30	0.98	0.31
Iso	1.66	0.48	1.92	0.51	1.51	0.40
Sevo	2.53	0.70	2.55	0.86	2.51	0.57
ETAgent (MAC multiple)						
Hal	1.23	0.39	1.51	0.33	1.09	0.34
Iso	1.29	0.37	1.49	0.40	1.17	0.31
Sevo	1.14	0.32	1.15	0.39	1.13	0.26

Table 3.4 Intraanaesthesia variables. Pooled values derived from all readings between 20 and 90min inclusive after induction.

HR: Heart rate
MAP: Mean arterial pressure
$ETCO_2$: End-tidal carbon dioxide concentration
ETAgent: End-tidal inhalant agent concentration
MAC: Minimum alveolar concentration (*Section 1.1.4.1)*
1.MAC = 0.90vol% (Hal), 1.29vol% (Iso), 2.22vol% (Sevo)

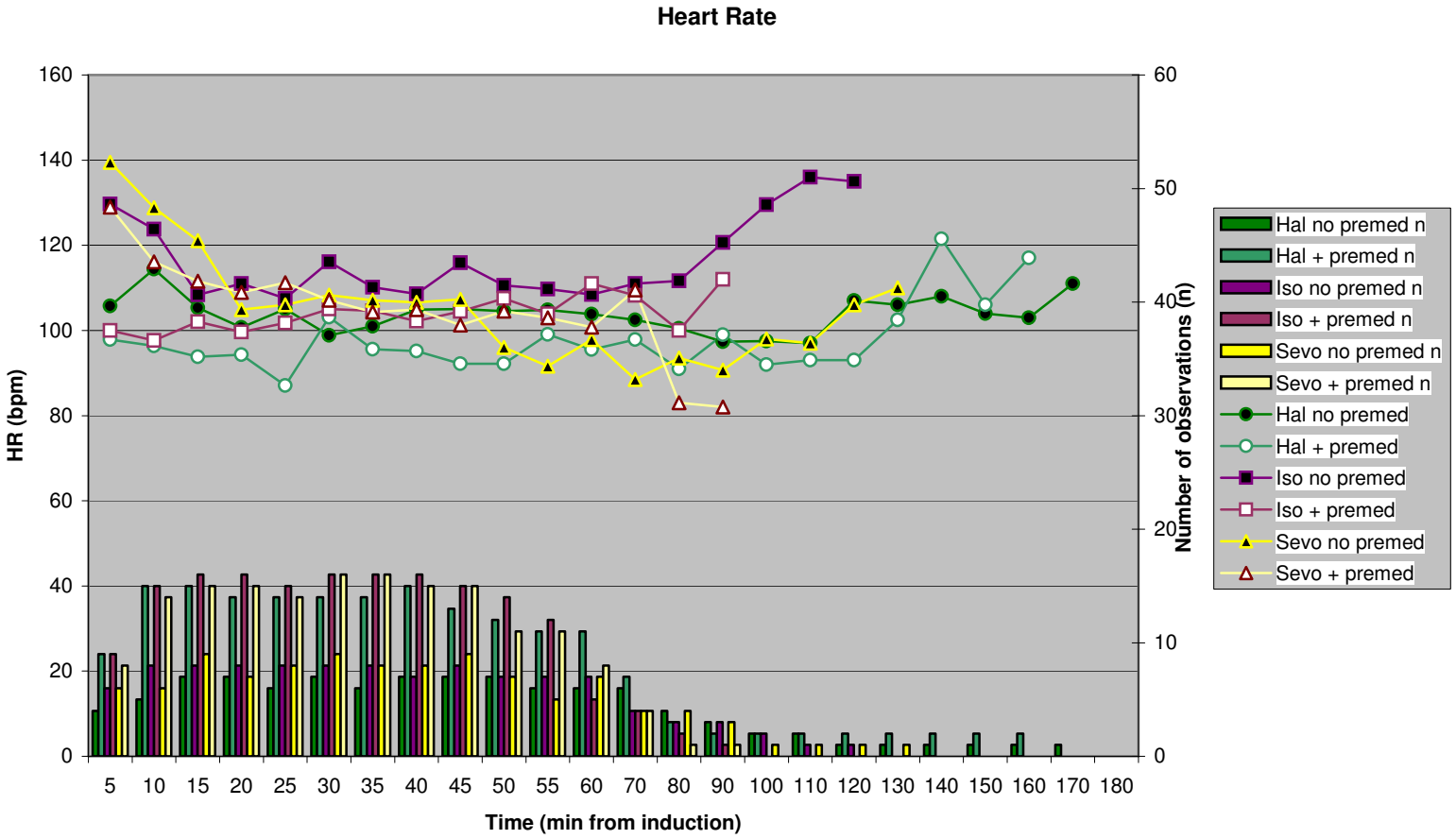

Figure 3.2: Heart rate in dogs anaesthetised using halothane, isoflurane and sevoflurane, with and without premedication

Columns: Number of data recordings per experimental group, total of 70 dogs
Lines: Mean values, heart rate

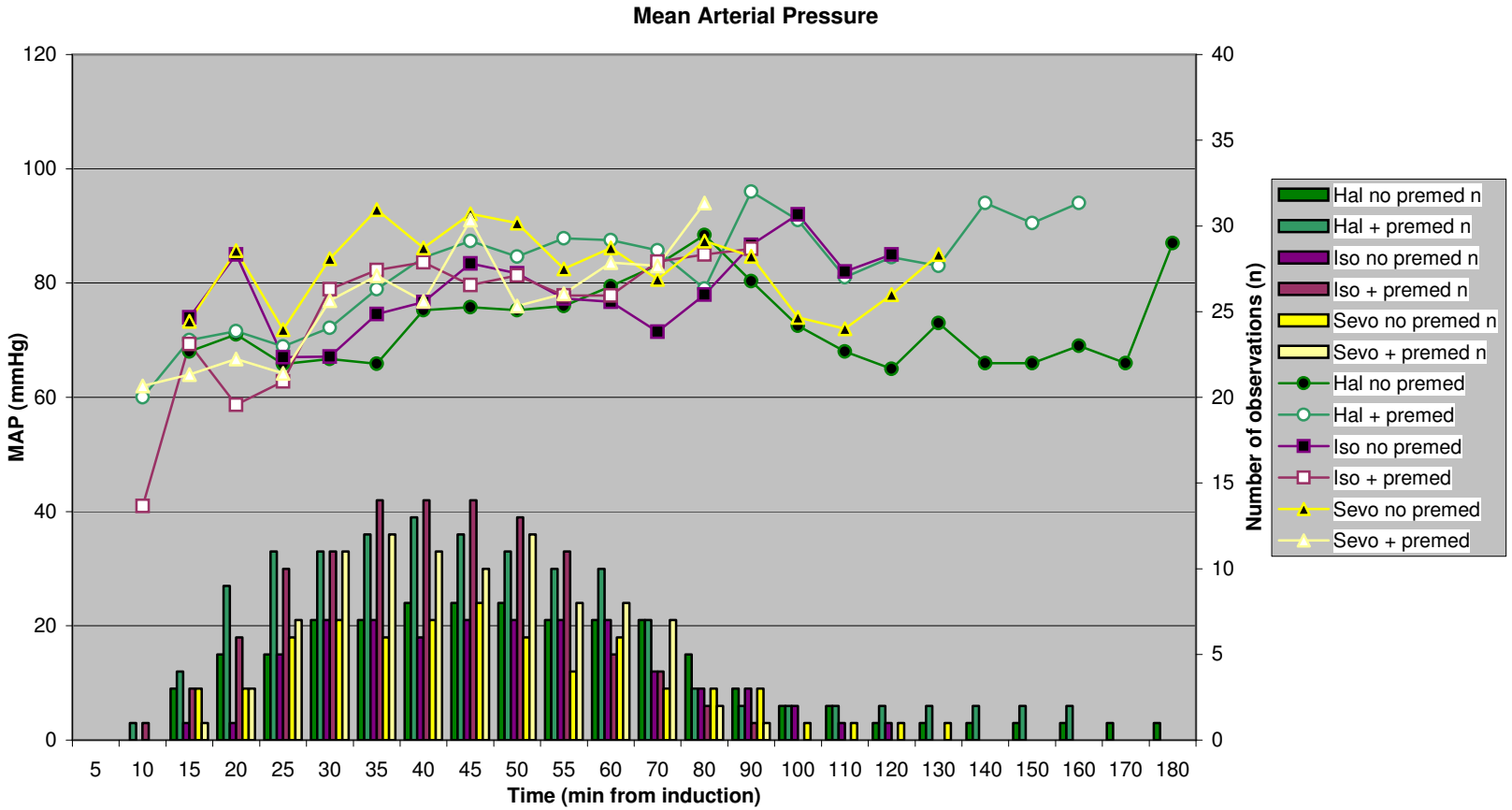

Figure 3.3: Mean arterial pressure in dogs anaesthetised using halothane, isoflurane and sevoflurane, with and without premedication

Columns: Number of data recordings per experimental group, total of 70 dogs
Lines: Mean values, Mean Arterial Pressure

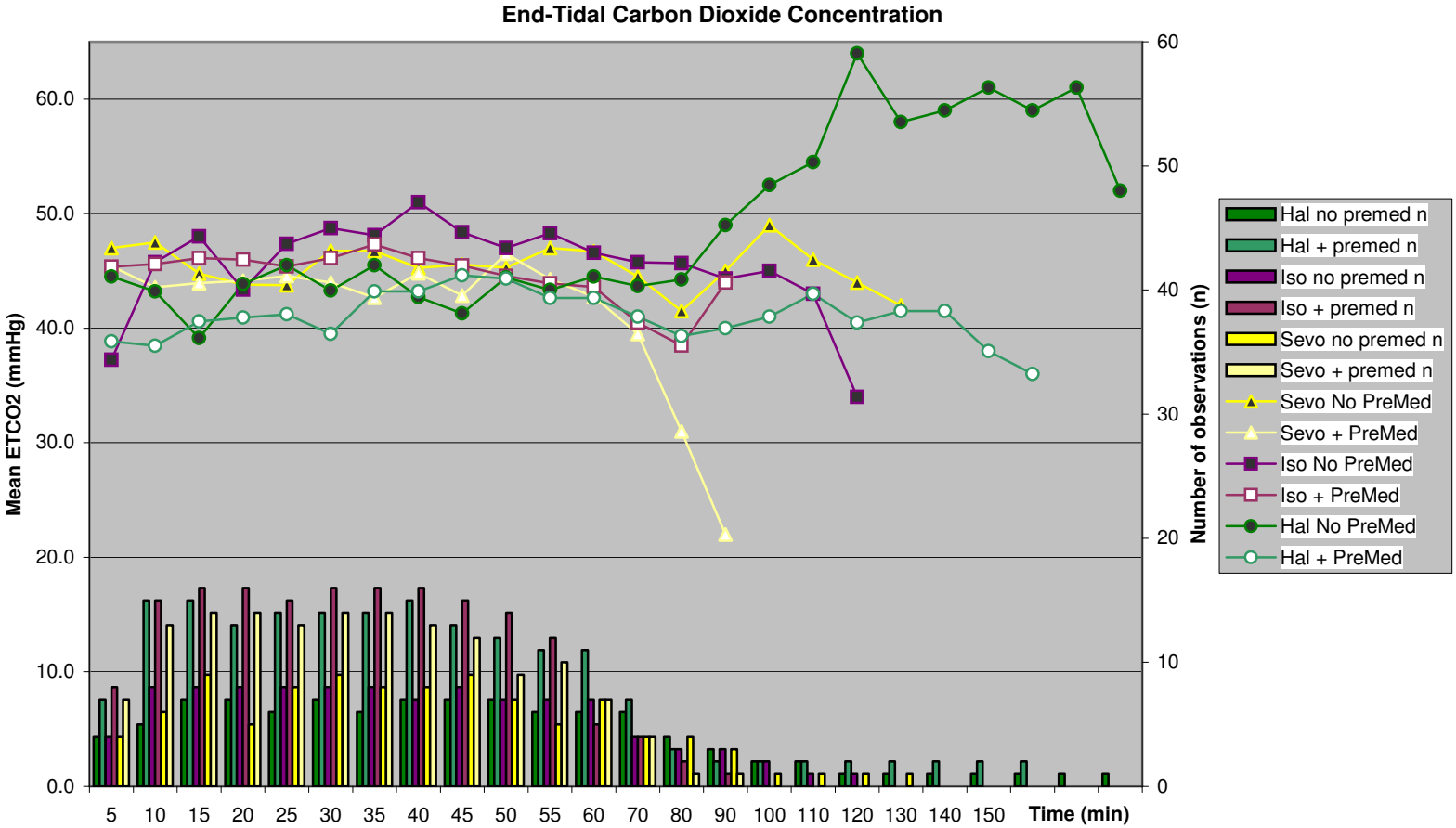

Figure 3.4: Mean end-tidal carbon dioxide concentrations in dogs anaesthetised using halothane, isoflurane and sevoflurane, with and without premedication

Columns: Number of data recordings per experimental group, total of 70 dogs

Lines: Mean values, end-tidal carbon dioxide concentration

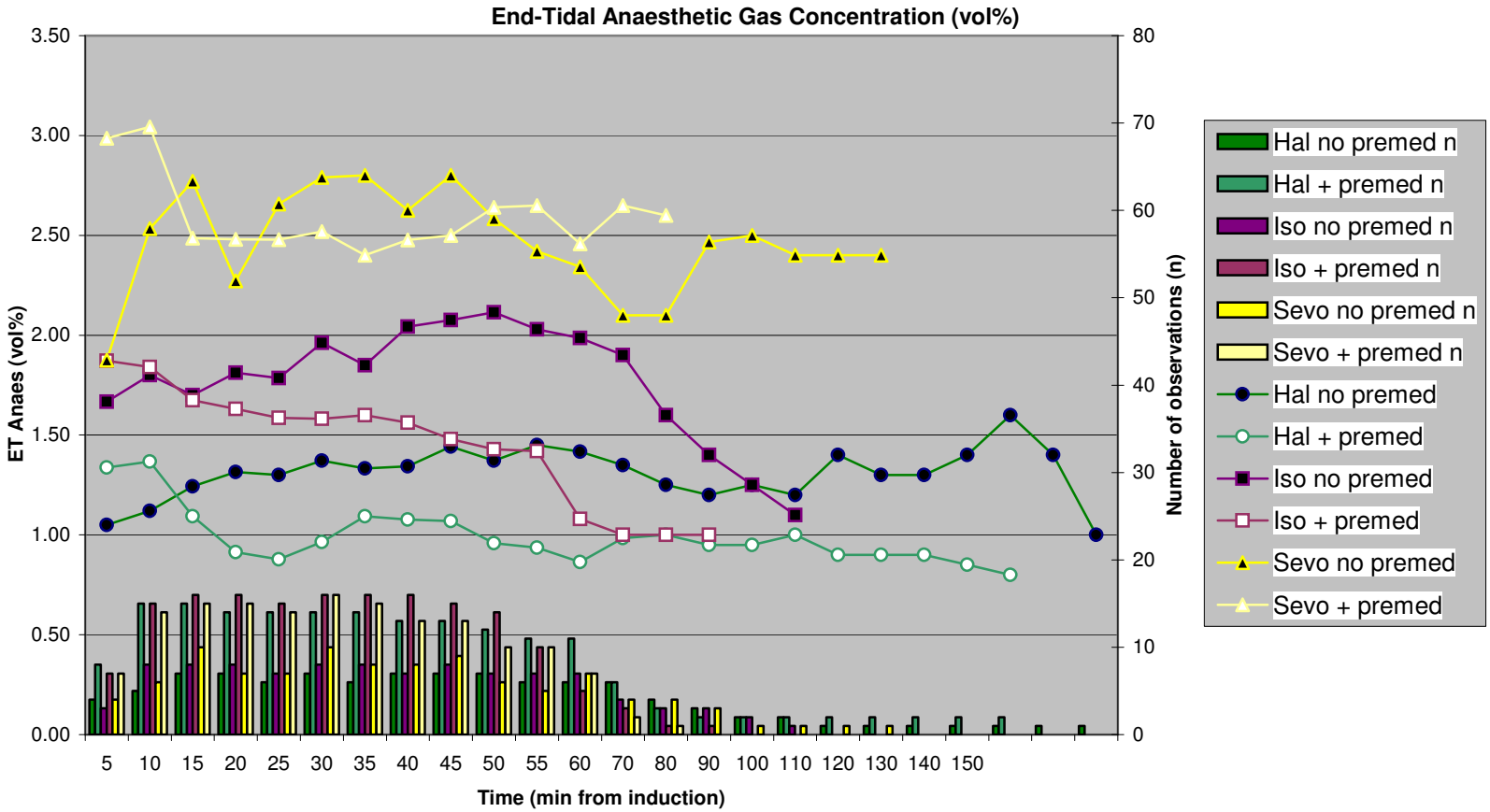

Figure 3.5: Mean end-tidal inhalant anaesthetic concentrations (vol%) in dogs anaesthetised using halothane, isoflurane and sevoflurane, with and without premedication

Columns: Number of data recordings per experimental group, total of 70 dogs
Lines: Mean values, end-tidal inhalant concentration

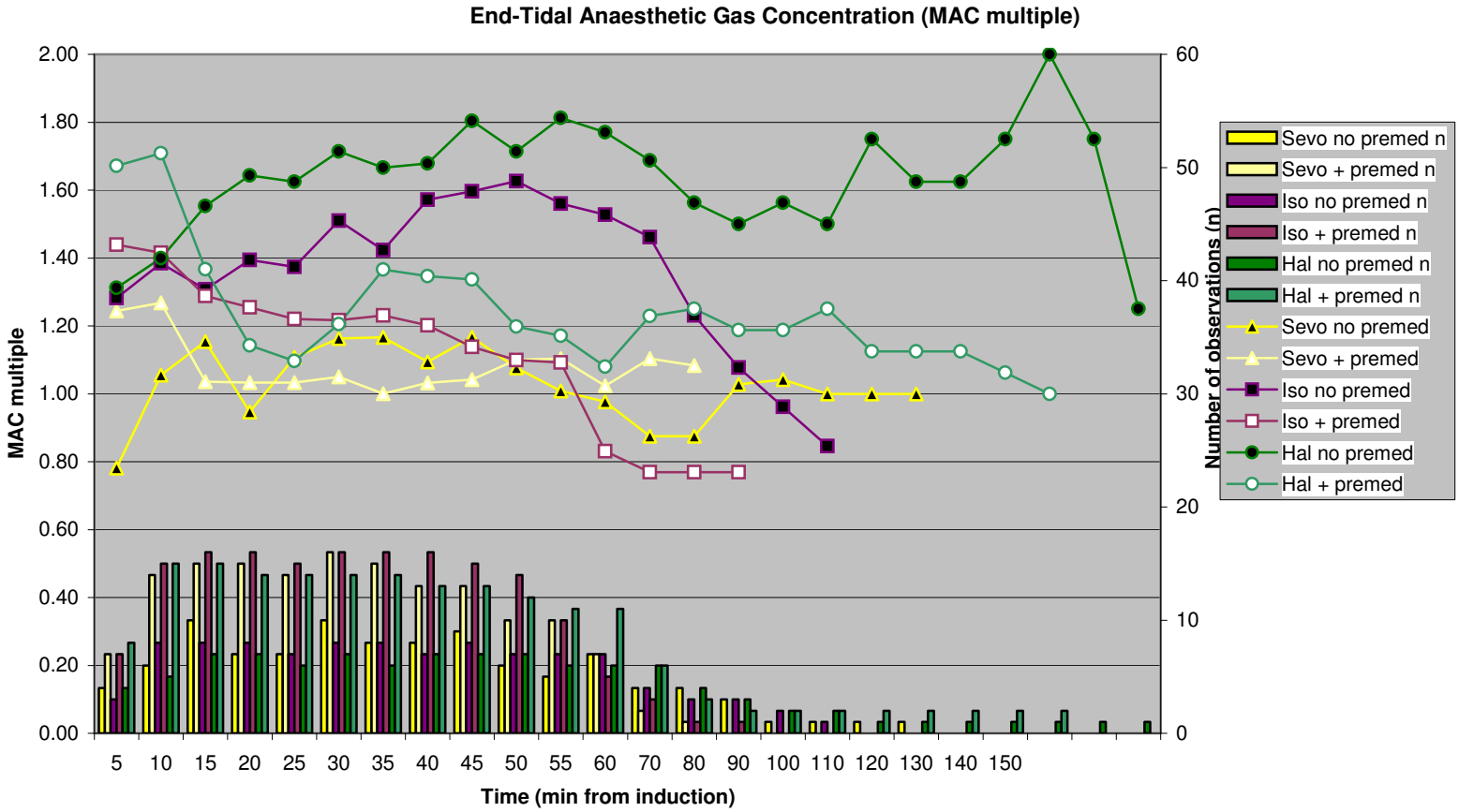

Figure 3.6: Mean end-tidal inhalant anaesthetic concentrations (MAC multiples) in dogs anaesthetised using halothane, isoflurane and sevoflurane, with and without premedication

Columns: Number of data recordings per experimental group, total of 70 dogs

Lines: Mean values, end-tidal inhalant anaesthetic concentration (MAC multiple)

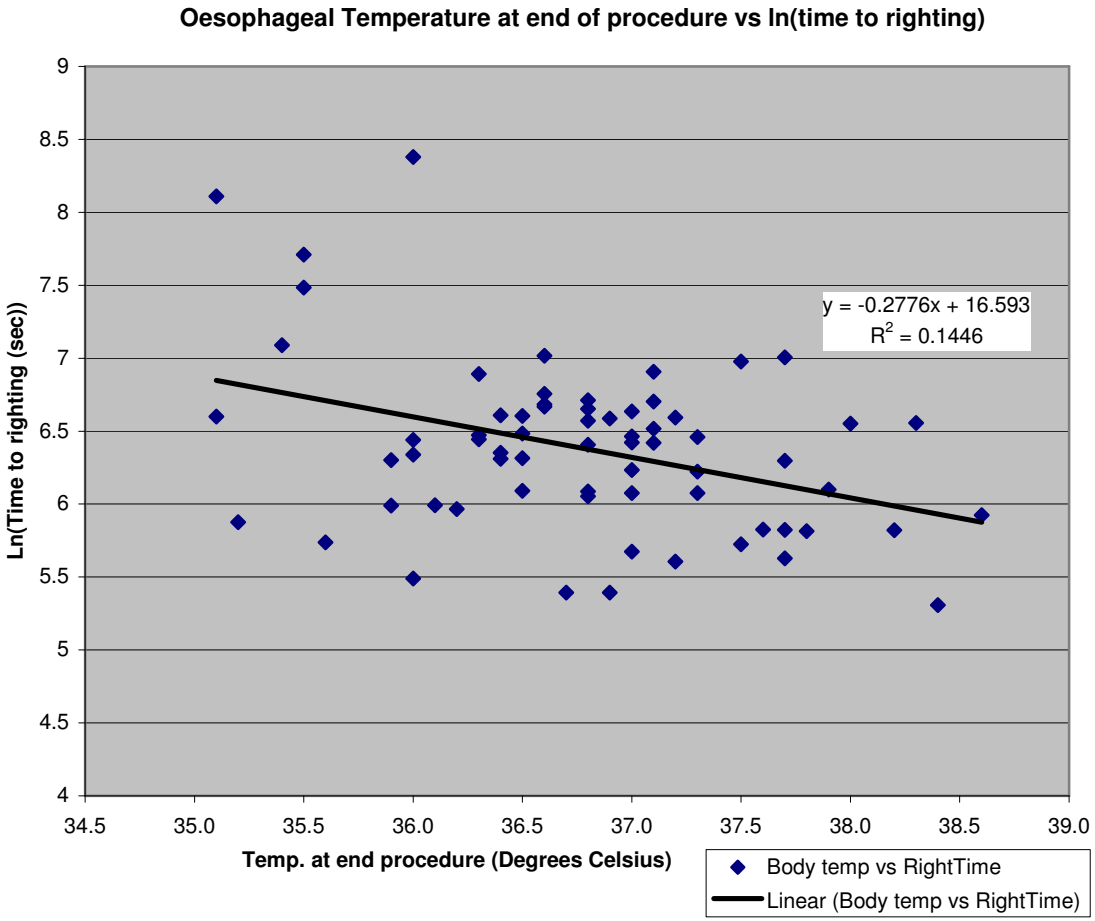

Figure 3.7 Oesophageal temperature at end procedure and its effect on recovery, in terms of time to righting
(n = 69)

3.6 Recovery from anaesthesia

Of the 71 dogs enrolled in the study, 69 contributed data related to recovery from anaesthesia. Data from the dog not desexed due to an abscessated wound was discarded. The recovery data from one other dog, anaesthetised with isoflurane after premedication, was not used. Confusion as to whether this dog also required a supplementary surgical procedure led to recommencement of isoflurane administration for 3-4min, placing it outside the recovery protocol outlined in Section 2.3.5.

3.6.1 Time to righting

The gaseous agent used for induction and maintenance of anaesthesia had no significant effect on the time to righting following anaesthesia.

There was no significant difference in time to righting between dogs induced with propofol and those in which anaesthesia was induced with a gaseous agent.

Dogs given premedication had significantly longer times to righting than those not given premedication (709.8 ± 58.3 vs 466.4 ± 48.6sec, p=0.003, *Figure 3.8*).

Oesophageal temperature at end of procedure had a significant effect on time to righting (p=0.006), with lower temperatures leading to longer times to righting (*Figure 3.7*).

Male dogs had significantly shorter times to righting than female dogs (498.2 ± 43.4sec vs 663.8 ± 69.9sec, p=0.05). The effect of sex on time to righting was not dependent on or modified by procedure time. Additionally, no significant interactions between sex and temperature were found.

3.6.2 Time to standing

The gaseous agent used had no effect on the time to standing after anaesthesia.

The use of propofol for induction of anaesthesia had no significant effect on the time to standing after anaesthesia, in comparison to dogs induced with a gaseous agent.

Dogs given premedication had a significantly longer time to standing than those not given premedication (1887.5 ± 189.1 vs 806.7 ± 84.9sec, p<0.001, *Figure 3.8*).

As for time to righting, male dogs stood significantly faster than female dogs (874.8 ± 96.4 vs 1742.4 ± 255.3sec, p = 0.001). Time of procedure had no significant effect on time to standing.

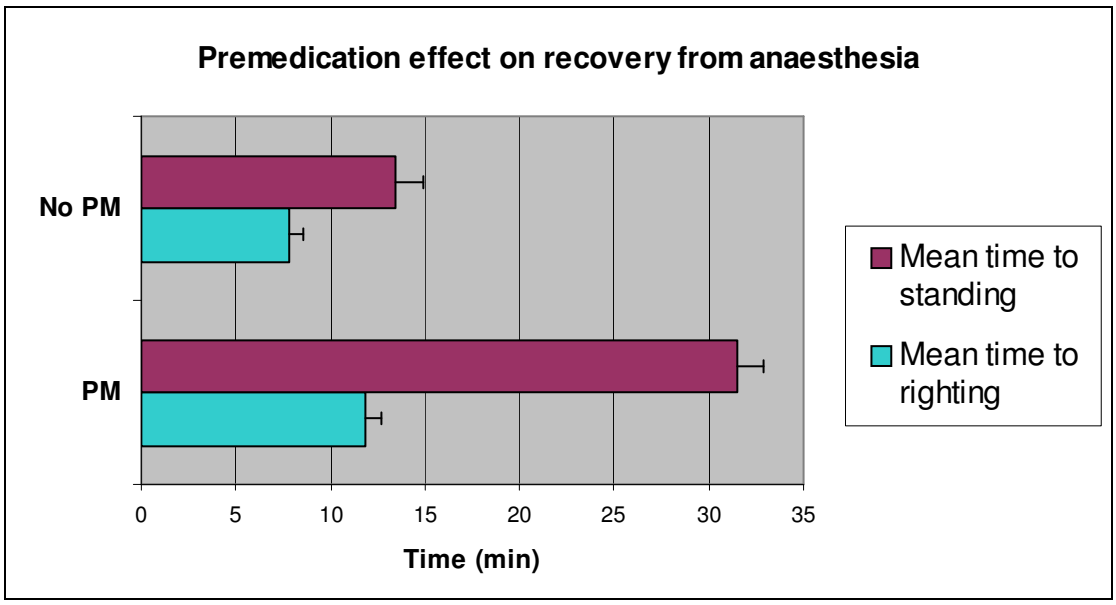

Figure 3.8 Effect of premedication on recovery from anaesthesia
No PM: No premedication
PM: Premedication

3.7 Cost of induction and maintenance of anaesthesia

The cost of induction with each of the three agents was calculated as described above (*Section 2.7*).

Inhalant induction cost a mean of A$0.42, A$1.47 and A$7.94 for halothane, isoflurane and sevoflurane respectively.

Intravenous induction with propofol after no premedication cost A$0.32 per kg body weight, A$4.59 for a dog of the mean weight in this study of 14.2kg, or

A$6.45 for a 20kg dog. When premedication was used, the reduced mean dose of propofol cost A$0.20 per kg body weight, A$2.84 for the 14.2kg animal, or A$4.01 for a 20kg dog.

Maintenance of anaesthesia, based on a vaporiser setting of 1.5.MAC for one hour with fresh gas flow of 1.0 $l.min^{-1}$, cost A$0.64, A$4.01 and A$21.40 for halothane, isoflurane and sevoflurane respectively.

Examples of reconditioned, agent specific precision vaporisers cost A$890, A$980 and A$1980 for halothane, isoflurane and sevoflurane respectively.

Chapter 4: Discussion

4.1 Introduction

The purpose of this clinical trial was to compare, in the clinical environment, i) the relative merits of the newer gaseous anaesthetic, sevoflurane, to those of isoflurane and halothane, and, ii) to compare induction of anaesthesia with these agents to induction with the intravenous agent propofol. Previous evidence in the experimental environment indicated induction with sevoflurane by mask would be faster and of better quality than that occurring with isoflurane or halothane, and potentially be comparable to induction with propofol.

4.2 Experimental design

The design of this trial allowed comparison of anaesthesia, particularly induction and recovery, between the three different inhalant agents and one intravenous agent, in the clinical environment.

The animals enrolled into this study were healthy adult dogs. Therefore the implications of this study should only be applied to a similar group of patients. The results occurring in other subgroups of patients in a normal veterinary practice, such as geriatrics, paediatrics and patients with systemic compromise from disease, may be considerably different. However, much of the growth in the use of inhalant induction in human practice has been in relatively healthy patients undergoing “day surgery”, and it is thus certainly justifiable to seek a better understanding of the effects of these agents in the equivalent group of veterinary patients.

Given the clinical nature of this study, a crossover design, as has previously been used in studies of induction and recovery from inhalant agents, was not possible. Therefore, larger numbers of animals were required in order to provide a reasonable likelihood of revealing differences between the various groups. Calculations of statistical power suggested minimum group sizes of 4 animals would provide an 80% likelihood of revealing significant differences in induction time between the three inhalant agents. This was based on the magnitude of the differences reported in previous studies. Group sizes of at least 4 animals were achieved. However, the

presence of factors such as the clinical environment (*Section 4.3*) complicated the outcomes.

It is perhaps worth speculating as to whether larger group sizes would have allowed more statistical differences to be discerned. Decreasing the total number of groups by decreasing the number of agents involved would have allowed larger numbers per group. This is further addressed below in relation to specific analyses, but overall, it would appear that very much larger group sizes would be required in order to produce differences between the various groups of statistical significance, if indeed such differences do exist.

The lack of blinding was a shortcoming in this study. One investigator administered the agents and marked the scores for the qualitative data with knowledge of the experimental group into which the dog had been placed. This introduces an unpredictable element of bias into the qualitative data which can not be removed. However, full double-blinding of this trial was considered infeasible given staffing and time constraints.

4.3 The clinical environment

Understanding the differences between the clinical and experimental environments is crucial to rationalising the disparity in several areas between the results of the current study and previous studies of induction and recovery comparing sevoflurane with isoflurane and halothane.

The methods used in this trial were designed to mimic circumstances found in a high quality private veterinary practice. The dogs were not acclimated to the induction room or procedures. During inhalant induction by mask, the maximum deliverable dose of the inhalant was used. It is common in clinical practice to use the maximum dose available from the vaporiser, in the assumption that the time to induction of anaesthesia will be minimised. As discussed below (*Section 4.4.1.5*), halothane was the main beneficiary of this dose selection. A previous experimental study of halothane and isoflurane induction in dogs could not discern a significant difference in speed of induction when equal concentrations, as opposed to equipotent doses, were used (Hellebrekers 1986). Although isoflurane is becoming more popular in private practice, halothane is still widely used and thus needed to be included in the

comparison. Dogs not receiving premedication were not given a placebo, likewise to mimic normal preanaesthetic procedure in a private veterinary practice.

Desexing is a common surgical procedure. Despite the analgesic effects of meloxicam, and, in some dogs, morphine, the persistent noxious stimulation following the tissue trauma of surgery will influence recovery. This is an important factor in the recovery from anaesthesia in animals in the clinical situation. Restricting enrolment into this study to dogs undergoing these two procedures minimised the variation in recovery based on differences in noxious stimulation during surgery. Using these routine procedures also allowed the duration of anaesthesia to remain generally within a small range.

In comparison, the two previous studies quantifying the differences between halothane, isoflurane and sevoflurane in dogs, in terms particularly of speed of induction and recovery, took place under very different circumstances. The studies by Mutoh, Nishimura *et al.* (1995) and Johnson, Striler *et al.* (1998) studies used Beagle dogs bred for research purposes. These dogs were anaesthetised more than once, as part of a crossover study design, and also in one study (Mutoh *et al.* 1995) for the placement of invasive monitoring equipment prior to the study proper. Although the full process of acclimation is not outlined in reports of these studies, the dogs involved were certainly given ample opportunity to become more accustomed to the procedure of inhalant induction of anaesthesia. This would likely decrease the psychological stress of the patient during inductions under study conditions. Lower, equipotent doses of inhalant were used, either 2.0.MAC (Johnson *et al.* 1998) or 2.5.MAC (Mutoh *et al.* 1995). During the maintenance period of anaesthesia, no procedures were performed on the dogs, excluding the effect of noxious stimulation on recovery from anaesthesia.

It is therefore likely the dogs of the current study were under more stress at the time of induction, and under greater levels of noxious stimulation during recovery. The effects of these factors are complex, and one can only speculate on the influence exerted upon the variables measured during this study. These factors may be considered as confounding factors, as they have made it more difficult to discern the effects of the inhalants themselves. However, the clinical environment represents the major area in which these agents are used, and therefore benefits seen only in the experimental situation may only be of limited value.

Whilst the disparity of these results, and specifically the inability of sevoflurane to display faster induction of anaesthesia than the older halogenated hydrocarbons, is no doubt due to many factors, the effect of the clinical environment stands tall above those areas discussed below. This issue represents a major hurdle for any new treatment introduced to veterinary practice. The uptake of sevoflurane by veterinarians, and particularly private practitioners, will no doubt be slowed if the experimental benefits of the newer, more expensive agent, can not make themselves clear in clinical patients.

4.4 Induction of anaesthesia

4.4.1 Time to induction

4.4.1.1 Introduction

The outcomes for time to induction of anaesthesia and quality of induction differed from what may have been expected. The greater speed of intravenous induction with propofol was in line with previous results. However, the lack of a significant difference in time to induction between those animals induced with sevoflurane by mask and those induced with either halothane or isoflurane was not consistent with two previous experimental studies.

Faster induction of anaesthesia is advantageous to ensure rapid control of the airway, minimising the likelihood of complications such as aspiration of regurgitated stomach contents. The complicating effects of excitation during induction are minimised with shorter inductions. Rapid induction of anaesthesia is also convenient in busy clinical situations.

4.4.1.2 Definition

The time from commencement of the induction process until endotracheal intubation was considered the best available measure of time to induction of anaesthesia. This measure has been used previously in studies of anaesthetic induction (Mutoh *et al.* 1995; Johnson *et al.* 1998). It provides a functional measure of time to induction of anaesthesia. Other methods used in human anaesthesia for defining induction of anaesthesia, such as cessation of finger tapping (Smith and Thwaites

1999), dropping a weighted object (Thwaites *et al.* 1997) and loss of response to verbal command (Smith *et al.* 1992) are not usable in the veterinary context.

4.4.1.3 Experimental group size

As discussed in Section 4.2, the size of the experimental groups limited the ability to illustrate significant differences between these groups. In the case of time to intubation, the statistical analysis suggests considerably larger groups may well have been required to demonstrate such differences. As an example, the ANOVA comparison for time to induction between dogs anaesthetised with isoflurane and those anaesthetised with sevoflurane yielded a p-value of 0.267. This is well away from the suggested threshold for significance of $p<0.05$.

4.4.1.4 Intravenous inductions

Inductions with propofol were significantly faster than inductions with a gaseous agent. This correlates with data from a study in humans (Smith and Thwaites 1999). Ultra-fast acting intravenous agents such as propofol or thiopentone possess a fundamental advantage over inhalant agents during induction in that a single bolus delivered over a few seconds can contain the entire dose required for completing induction of anaesthesia. This creates the most rapid rise in plasma concentrations possible, giving every opportunity for fast induction. Inhalant agents generally require many breaths over a period of a minute or more to deliver sufficient agent into the plasma and target tissues. In humans, the low solubility and relatively pleasant odour of sevoflurane make possible induction of anaesthesia from a single, large breath (Agnor *et al.* 1998). However, this procedure is not possible in dogs.

4.4.1.5 Halothane dosage

Higher doses of halothane were used for induction of anaesthesia in this study than have been previously used. The maximum output of a Tec 3 halothane vaporiser as used in this study is 5%, which equates to approximately 5.4.MAC for halothane. In comparison, doses of 3.8 and 3.4.MAC of isoflurane and sevoflurane respectively represented the maximum available output from the agent-specific vaporisers used.

As discussed above (*Section 4.3*), veterinarians commonly use the maximum output of the vaporiser during inhalant induction of anaesthesia via mask. There is no clear contraindication for using this dose of halothane during induction, provided that the patient is monitored to ensure the depth of anaesthesia does not become excessive in the minutes following intubation.

The resultant times to intubation for halothane were significantly faster than those reported previously in comparisons with other agents. As an example, Mutoh, Nishimura *et al.* (1995) used 2.5.MAC halothane in unpremedicated dogs and recorded a mean time to intubation of 821.3sec. In the present study, unpremedicated dogs induced with halothane were intubated in a mean time of 225.6sec. Likewise, mean differences between halothane induction and isoflurane or sevoflurane induction of only 49 and 25sec respectively are considerably smaller than those reported using equipotent doses of the inhalants (Mutoh *et al.* 1995).

4.4.1.6 Failed inhalant inductions

Two dogs were placed into groups for inhalant induction without premedication but were unable to be satisfactorily induced with the selected agent. These posed certain problems. There was no satisfactory way to include these two cases in the statistical analysis of time to intubation. Although time to intubation was recorded for these cases, each was actually induced with propofol after some delay, and clearly this time bore no relation to those recorded for other animals in the same groups. Imputing a value for time to intubation for these dogs reflecting the slow, unsatisfactory induction of anaesthesia would have been artificial and impossible to undertake objectively. Therefore these two were excluded from the analysis, and the subsequent analysis results must be viewed with that point in mind.

Thus it would appear that the analysis of time to intubation has been biased towards shorter times to intubation in the two groups in which failure of inhalant induction of anaesthesia occurred. The agents in these two cases were isoflurane and sevoflurane. The resultant analysis showed sevoflurane induction not to be significantly different from halothane or isoflurane inductions in terms of time to intubation. Thus the failed induction with sevoflurane should have no bearing on the validity of this result. Time to intubation for dogs induced with isoflurane was significantly faster than for those induced with halothane. The p-value for this

analysis being well below the threshold for significance, it is unlikely the omission of one failed induction with isoflurane affects the validity of this result.

The implications of the two failed inductions with inhalant agents extend further than simply the statistical analysis. It would appear that in the clinical environment, not all dogs are suitable for induction of anaesthesia by an inhalant agent, particularly without premedication. A previous study of sevoflurane in clinical veterinary use described mask induction with this agent in 5 cases, however, no comment as to failed inductions, or the quality of inductions, was made (Haitjema and Cullen 2001).

Both of these cases were in groups receiving no premedication. Both of these dogs, as well as the other 69 cases, submitted to the procedure of intravenous catheter placement prior to induction. The fact that these dogs were considered sufficiently calm on initial examination to be placed into no-premedication groups suggests that it may be difficult to determine before mask application which dogs will be unsuitable for inhalant agent induction. However, it should also be noted that these dogs originated from Blacktown Pound, and hence were potentially more likely to have underlying behavioural problems when restrained and handled. The success of inhalant induction of anaesthesia in a private practice environment will no doubt rest upon the population of animals on which it is used.

4.4.1.7 Effect of premedication

An improvement in speed of induction of anaesthesia was expected with the addition of premedication to the induction protocol, and was reflected in the results of the present study. However, the active selection of animals into groups for premedication makes interpreting these results somewhat more difficult.

A basic assumption of the analysis of variance statistical method is that all animals have been randomly allocated into the experimental groups. Whilst this was the case for induction method and agent used in the current study, the dogs enrolled were not randomly allocated premedication. Dogs that were more excitable, nervous or hard to handle at the initial assessment of demeanour were placed into groups to receive premedication, those that were calmer were allocated to a group not receiving premedication (*Section 2.5.1.2.1*). Therefore, the effects shown in the statistical analysis as being due to premedication are not due to premedication alone, but also

due to the characteristics of the animals selected into the premedication groups. This should be considered when assessing the results.

The use of acepromazine or morphine has been shown to decrease dose requirements for anaesthesia either with propofol or the inhalant agents (Pugh 1964; Raiha *et al.* 1989; Steffey *et al.* 1993). Lower dose requirements should be more rapidly achieved under the induction protocols used in the current study. Overall, animals premedicated showed a significantly faster time to intubation than animals not premedicated. However, when comparing the individual induction agents separately, only propofol showed a significant improvement with the addition of premedication. This may be indicative of the small group sizes of animals induced with inhalants without premedication, as compared to the larger number of dogs induced with propofol.

Animals under more psychological stress at induction are expected to have slower and poorer quality inductions. It is therefore noteworthy that the group of animals exhibiting more signs of nervousness prior to anaesthesia was, after application of premedication to this group, the animals that were more rapidly induced. It would seem likely that had the premedication been randomly allocated, its effect may even have been stronger than shown in this study.

4.4.1.8 Clinical significance

The clinical significance of these results must also be considered. It is difficult to determine whether the mean 49sec difference between isoflurane and halothane in terms of time to intubation is of importance to the veterinarian administering the agent in private practice, especially given the lack of difference between the agents in terms of quality of induction. More so for sevoflurane, given that the mean time to intubation for the newest agent falls midway between the other inhalants. Although significantly faster for induction in the experimental environment, this study does not objectively identify any benefits to its use in the clinical situation for inhalant induction of anaesthesia, in the subgroup of healthy, young patients as enrolled herein.

4.4.2 Quality of induction

The lack of significant difference between the inhalant agents in terms of quality of induction was unexpected. Expected, however, was the improvement in quality provided by premedication, and by induction with propofol over the inhalant agents. The clinical environment, as discussed above (*Section 4.3*), assumes a major role rationalising these results. Variations in each dog's response to handling, intravenous catheter placement, placement of the induction mask, or other factors unknown, appear to assume greater importance than the variation between the three inhalants in terms of irritancy to the respiratory tract.

Sevoflurane has previously been reported to give an improved quality of induction of anaesthesia over isoflurane in dogs (Johnson *et al.* 1998). It is suggested that this is due to sevoflurane's lower irritancy to the respiratory tract, which leads to lesser decreases in tidal volume and minute volume on inhalation (Doi and Ikeda 1993), combined with sevoflurane's lower blood:gas solubility allowing faster changes in concentrations at the level of the CNS. The lack of difference between any of the three inhalants in the present study therefore demands explanation.

4.4.2.1 Measuring quality

All measures of quality of induction of anaesthesia are in essence subjective. The scale used to record this variable in this study has not been previously reported, although it is similar to that used by Johnson *et al.* (1998) in several of the behaviours on which the final score was based. Basing the score for quality of induction on several areas of behaviour exhibited by the animal provided more consistency to the scoring process. However, until the dog is able to converse on equal terms with the investigator to explain its experience of the process of induction of anaesthesia, all descriptions of quality of induction will be limited.

More information on the animal's response to induction may have been provided by the use of invasive monitoring of variables such as arterial blood pressure and oxygenation from before the commencement of induction. However, requiring previous general anaesthesia or at least deep sedation, placement of such instrumentation would not have been possible within the design of the study.

4.4.2.2 Effect of premedication

The improvement in quality of induction in dogs receiving premedication over those not receiving premedication was expected. Premedication with agents such as acepromazine and morphine is commonly used for the specific purpose of improving the perceived quality of anaesthesia, as well as decreasing the induction agent doses required. Premedication should have decreased the psychological stress involved with induction of anaesthesia. The use of agents such as acepromazine prior to anaesthesia is also thought to minimise or completely remove the involuntary excitation phase of anaesthesia, with a consequent significant improvement in the perceived quality of anaesthesia.

4.4.2.3 Intravenous inductions

Inductions with propofol were of significantly better quality than inductions with an inhalant agent. Propofol inductions have been previously noted to completely bypass the excitation phase of anaesthesia (Watkins *et al.* 1987), and this was borne out in the results of the current study. However, a previous study in humans showed that anaesthetists blinded to the agent being used for induction of anaesthesia were not able to reliably judge whether sevoflurane by mask or a target-controlled infusion of propofol was being used (Smith and Thwaites 1999).

No patients assigned propofol for induction failed to be satisfactorily anaesthetised with the intravenous agent, and propofol proved a satisfactory fall-back for those patients unable to be induced using inhalants. Although the necessity of intravenous access is sometimes considered a drawback, propofol remains a reliable agent for smooth, high quality induction of anaesthesia.

4.5 Recovery

4.5.1 Introduction

An improvement in the speed and quality of recovery may have been expected in those animals maintained on the newer, less soluble inhalant agents isoflurane and sevoflurane. This was not borne out by the results. Reasons for these results cover

similar territory to that discussed under Sections 4.2 and 4.3. The improvement in speed of recovery, in terms of time to righting, with animals with higher body temperature, was a result with notable clinical significance.

4.5.2 Time to righting and standing

Several studies of recovery from anaesthesia in humans, as summarised by Patel and Goa (1996), indicate more rapid emergence following the use of sevoflurane, when compared to isoflurane in adults. Likewise, recovery in children is faster following the use of sevoflurane, compared to halothane. However, this has not been demonstrated in dogs, with Johnson, Striler *et al.* (1998) finding no difference between the recoveries of dogs anaesthetised with sevoflurane and those anaesthetised with isoflurane in a MAC determination study. This was supported by the current study, with the maintenance inhalant agent exerting no significant effect on recovery. These results indicate factors other than choice of inhalant agent exert the major influences on the speed and quality of recovery from anaesthesia in dogs.

4.5.2.1 Duration of anaesthesia

Within the range of procedure times recorded during this study, the duration of anaesthesia had no effect on the speed or quality of recovery. The mean time of anaesthesia, from induction to end procedure, was approximately 70min in this study. The choice of agent may have greater effect in procedures lasting considerably longer than this time, as it is likely the recovery from more soluble agents such as halothane is more elongated after such periods.

4.5.2.2 Choice of induction agent

The choice of either propofol or an inhalant agent for induction had no effect on the speed or quality of recovery. This is expected, as propofol is an ultra-short acting agent. Recovery in dogs given propofol sufficient only to induce anaesthesia was judged complete in approximately 20minutes (Watkins *et al.* 1987). The duration of anaesthesia in the current study was considerably longer. The residual effects of propofol should be minimal by this time, exerting a negligible effect on recovery.

4.5.2.3 Effect of premedication

Anaesthetic protocols including the use of premedication led to significantly longer mean times to righting and standing in recovery. Given that the mean anaesthesia time in the current study was 70min, and dogs in the groups receiving premedication were given the acepromazine and morphine combination approximately 30min prior to induction, it was expected that both these drugs would still be exerting an effect on the animal during recovery. The effects of acepromazine and morphine are each expected to last 3 – 4hr (Pugh 1964; Branson and Gross, 2001).

In isolation, the tranquillising effects of acepromazine lead animals to assume "voluntary recumbency" (Pugh 1964), and therefore it is not surprising that dogs given acepromazine tended to take longer to stand after anaesthesia than dogs not given the drug. Animals experiencing discomfort postoperatively may stand or pace. Hence, dogs receiving the potent analgesic morphine would be less likely to show this behaviour postoperatively.

From this, it becomes apparent that fast recoveries are not *per se* good recoveries. Animals that stand or move about soon after cessation of anaesthesia may in fact be demonstrating signs of pain, rather than benefiting from the rapid clearance of the anaesthetic agent. Adequate analgesia should not be withheld from a patient in order to produce a faster recovery.

The clinical significance of the longer times to righting and standing after anaesthesia in the current study is likely very limited. The mean times to righting and standing for premedicated dogs were 709.8 and 1887.5sec respectively, or 11.8 and 31.5min. These are relatively short periods, unlikely to interfere with the flow of work through a private practice or slow the discharge of a patient following desexing, and are probably indicative of the close attention paid to depth of anaesthesia and body temperature in these dogs.

4.5.2.4 Effect of body temperature

Although, in the personal experience of the author, dogs that become hypothermic have longer and poorer quality recoveries, no such study involving dogs

has been published. In the current study, animals which had lower body temperatures at the end of the procedure had significantly slower recoveries. Decreasing body temperature decreases the dose requirement for inhalant anaesthetics (Eger 1996). It should thus be expected that the time to recovery for hypothermic animals will be delayed. Hypothermia also slows the rate of metabolic processes within the liver and other tissues of the body, and decreases the minute respiratory volume (Mets 2000; Mallet 2002). Decreased body temperature may also depress cardiac function (Guyton 1991; Mallet 2002). These effects will further slow the clearance of anaesthetic agents from the patient.

Hypothermia is a major complication of surgery in small animals, particularly in the private practice situation. Conservation of body heat was a consideration within the design of this study, with the use of heat lamps on dogs after premedication and during recovery. Heat mats were used both during preparation for surgery, and surgery. The mean body temperature at end procedure (36.8 ± 0.8°C, mean ± SD) indicates these measures were generally successful. Nonetheless, even within this relatively benign range of body temperatures, a significant shortening of recovery time, in terms of time to righting, occurred with higher body temperature. It is likely that this effect would be even more pronounced with more extreme degrees of hypothermia.

4.6 Intra-anaesthesia variables

4.6.1 Biological significance

Given the nature of the results recorded in relation to the cardiorespiratory variables measured during anaesthesia, further discussion should be preceded by consideration of their biological, or clinical, significance.

Heart rate, end-tidal carbon dioxide and mean arterial blood pressure are variables measured frequently in clinical veterinary anaesthesia. As with all variables measured in veterinary science, ranges of values considered “acceptable” have been produced, reflecting the domain in which the patient is least likely to experience intra-anaesthetic or post-anaesthetic complications. Acceptable heart rates are contingent upon the size of the dog, but may be considered as 60 – 140bpm. For end-tidal carbon

dioxide, the acceptable range used at the UVCC, and reflecting reports in the literature, is 35 – 50mmHg. For mean arterial blood pressure, 60 – 110mmHg.

All mean readings for these three parameters for each of the three inhalants, as described in Table 3.4, are within these acceptable ranges. Therefore, it is difficult to ascribe any clinical significance to any of the differences between the three inhalants based on these results. Further statistical analysis of this data was thus considered unnecessary and potentially misleading.

4.6.2 Heart rate

Induction and maintenance of anaesthesia with sevoflurane has been previously associated with significant elevations in heart rate in comparison particularly to halothane (Harkin *et al.* 1994; Mutoh *et al.* 1995; Mutoh *et al.* 1997; Polis *et al.* 2001). Whilst Figure 3.2 indicates higher heart rates in the early minutes after induction, heart rates through the maintenance period of anaesthesia were similar for all three agents.

The lack of obvious impact of the use of acepromazine and morphine as premedication should be noted. Both of these drugs have been shown to decrease heart rate (Popovic *et al.* 1972; DeSilva *et al.* 1978; Boyd *et al.* 1991; Kojima *et al.* 1999), and it would be logical to consider that the analgesic effects of morphine would also produce lower heart rates during surgery. This was not noted, with the mean values for no-premedication and premedication groups for each inhalant being within one standard deviation of each other.

Whilst anecdotal evidence indicates that heart rate increases at incision, this was not noted in the current results. This was most likely due to incision not occurring at a consistent time relative to induction, with the effect of incision therefore being spread over several data points. Further, with heart rate data collected only every 5min, transitory increases may not have been recorded at all.

4.6.3 End-tidal carbon dioxide concentration

End-tidal carbon dioxide concentration was considered the most useful single indicator of respiratory function available within the limitations of the clinical

environment, as commonly used in previous studies (Mutoh *et al.* 1995; Steffey 1996; Mutoh *et al.* 1997).

Isoflurane and sevoflurane have previously been shown to depress respiratory function more than halothane, in terms of $ETCO_2$ readings (Mutoh *et al.* 1995; Steffey 1996; Mutoh *et al.* 1997). Whilst values for $ETCO_2$ in the current study tended to be slightly higher for isoflurane and sevoflurane than halothane, only one mean reading during the 20 – 90min maintenance period of anaesthesia exceeded the acceptable range for $ETCO_2$ (*Section 4.6.1*), with the 40min reading for the group anaesthetised with isoflurane without premedication being 51.0mmHg. All other readings during this period remained within the 35 – 50mmHg acceptable range.

Again, the lack of effect of premedication with acepromazine and morphine was noteworthy. Respiratory depression is an oft noted effect of morphine (Steffey *et al.* 1993). The lack of difference between the premedicated and non-premedicated animals in the current study may be due to the doses of morphine being considerably lower than those used in previous studies (Steffey *et al.* 1993), and to the confounding effects of the stimulus of surgery.

4.6.4 Mean arterial blood pressure

Whilst by no means the best single indicator, mean arterial blood pressure does illuminate elements of the health of the cardiovascular system under anaesthesia. MAP values were derived using the gold standard of intraarterial catheterisation. A more complete picture of the effects on the cardiovascular system by anaesthesia would have been produced by measurement of cardiac output, cardiac contractility and systemic vascular resistance. However, this would have required much more invasive testing, and was not compatible with the clinical nature of this study.

MAP values have been shown to be generally lower with sevoflurane and isoflurane in comparison to halothane anaesthesia, although establishing statistically significant differences has eluded several studies (Steffey and Howland 1978; Bernard *et al.* 1990; Frink *et al.* 1992a; Murray *et al.* 1992; Harkin *et al.* 1994; Malan *et al.* 1995; Mutoh *et al.* 1995; Holzman *et al.* 1996; Mutoh *et al.* 1997; Grosenbaugh and Muir 1998). In the current study, all three agents were closely grouped in terms of MAP values through the 20 – 90min segment of anaesthesia where the largest amount of data was available, and only one mean MAP point was below the minimum

acceptable range (*Section 4.6.1*) for MAP, with the 20min reading for dogs anaesthetised with isoflurane after premedication being 58.7mmHg.

Again, the results indicated that the use of acepromazine and morphine had little effect on the MAP. Acepromazine has been variably associated with depression of MAP due to vasodilation (Popovic *et al.* 1972; Turner *et al.* 1974), and morphine should have similar effects (DeSilva *et al.* 1978; Given *et al.* 1986). Again, the effect of lower doses in comparison to previous studies, and the effects of surgical stimulus combine to produce the likely explanation for these results.

4.6.5 End-tidal inhalant anaesthetic agent concentration

Unlike the other intraanaesthesia variables measured, end-tidal inhalant anaesthetic concentrations (ETA) are not a measure of the animal's physiological status under anaesthesia. ETA instead is the most accurate clinical means of determining the dose of the inhalant that is acting upon the patient. As expected, these readings varied widely between the three different agents.

Halothane is a more potent anaesthetic agent than isoflurane, which in turn is more potent than sevoflurane. A higher concentration of a less potent agent must be delivered to provide the same effects in comparison to a more potent agent. The differing potencies of the three agents are reflected in their MAC values (*Table 1.2*). The dose requirement for normal surgery is expected to be at least 1.2 to 1.4.MAC (Steffey 1996). The MAC is influenced by many factors, the presence of drugs other than the inhalant and the core temperature of the animal being the most important factors in the current study.

The mean ETA values measured in the current study for dogs anaesthetised with halothane or isoflurane without premedication represented 1.51 and 1.49 times previously established values for MAC for the respective agents. In those patients induced with propofol, it would be expected that the influence of this drug should have passed by 20min after induction, the time from whence measurements of ETA were used for these calculations. Approximately 1.5.MAC is in line with the previously discussed requirements for normal surgery in dogs (Steffey 1996). However, patients anaesthetised with sevoflurane without premedication required only a mean of 1.15.MAC over the same period.

Acepromazine and morphine have each been shown to decrease the MAC for isoflurane or halothane by more than 40% (Heard *et al.* 1986; Steffey *et al.* 1993). Patients anaesthetised with halothane or isoflurane after premedication required 28.1% or 21.7% less of the respective inhalant than those not premedicated. Again, these results were in line with expectations from previous literature on depression of MAC by these agents. However, there was effectively no change in the concentration of sevoflurane required by premedicated animals, at 2% less than non-premedicated animals.

The lower overall requirement for sevoflurane, in comparison to its established MAC value, and the lack of reduction of sevoflurane dose requirement following premedication is somewhat of a mystery to the author. There is no obvious explanation. Operator bias could potentially be involved, possibly involving closer examination of the depth of anaesthesia and vaporiser settings when using the less familiar agent. This, however, can only be speculation.

4.7 Financial considerations

Private veterinary practice is sensitive to costs involved in anaesthesia. As outlined above, the newer inhalant agents increase the overall cost of anaesthesia due both to their increased price per unit volume, and their higher dose requirements, compared to halothane. Whether this cost can be absorbed into charges passed onto the client in normal veterinary practice will vary greatly between practices, and is beyond the scope of this thesis to discuss. However, it is evident that the lack of clear advantage to the use of an agent such as sevoflurane in routine cases, such as desexing, would make many private practitioners loth to purchase the more expensive product.

The impact of the much greater cost of the sevoflurane vaporiser in comparison to those for halothane or isoflurane will vary widely between practices, based on the number of cases seen and overall financial arrangements.

The maintenance of anaesthesia costs outlined above should be used primarily for comparison between the agents, and will in many cases overestimate the actual consumption of inhalant. In the current study, the minimum fresh gas flow of 1.0 $l.min^{-1}$ was used due to the loss of at least $500ml.min^{-1}$ to the monitoring equipment.

With more efficient monitoring, a minimum gas flow of 500ml.min^{-1} is quite acceptable in a rebreathing system, provided this supplies at least 20ml.kg.min^{-1} (Steffey 1996). Such a gas flow rate would immediately halve the described maintenance cost. Premedicated animals in the current study were often able to be maintained on vaporiser settings equal to less than 1.5.MAC for the specific agent, similarly reducing the cost of the agent for maintenance of anaesthesia. During the transition phase from an intravenous induction to a inhalant maintenance of anaesthesia, vaporiser settings when using the more insoluble isoflurane and sevoflurane may be more rapidly decreased to a maintenance level, due to the more rapid rise in target tissue concentrations with these agents. This in turn would decrease the cost of these agents relative to halothane.

Despite these considerations, it may be assumed that sevoflurane will retain a considerable cost premium over the older agents for the foreseeable future.

4.8 Conclusion

This study was undertaken to test four hypotheses as outlined in Section 1.6. Essentially these focussed upon elucidating the differences between halothane, isoflurane, sevoflurane and propofol when used for induction and maintenance of anaesthesia in dogs undergoing the common clinical procedure of desexing.

Previous studies of human and veterinary anaesthesia indicated that mask induction using sevoflurane resulted in significant advantages in terms of the speed and quality of induction, when compared to either halothane or isoflurane. Likewise, the medical literature points towards faster recoveries with the newer agent. Such results are in line with the basic chemical properties of these agents. However, the veterinary literature is limited in comparison to the medical literature, with no quantitative, comparative studies of this topic undertaken in the clinical context.

This study showed no advantages for the use of sevoflurane over either halothane or isoflurane. The speed of induction using sevoflurane was not significantly different from that seen with either halothane or isoflurane. Induction of anaesthesia using isoflurane by mask was significantly faster than induction using halothane by mask. Choice of inhalant for induction did not improve the quality of induction, as perceived by the veterinarian administering the agent. However, the use

of propofol was associated with significantly faster inductions and an improved quality of induction. During the maintenance phase of anaesthesia, standard cardiorespiratory variables remained within normal ranges for all three inhalants. Speed of recovery from anaesthesia was not affected by choice of inhalant or induction method, but was increased by improving core temperature at the end of the procedure. The use of premedication slowed the time to righting and standing.

All studies are limited. The current study involved a total of 12 experimental groups, a result of comparing three different inhalants and one intravenous agent. This produced smaller numbers in each group, limiting the ability to detect significant differences between the groups. Although the importance of this problem is questionable, further study focussing on comparing, for example, isoflurane and sevoflurane in premedicated dogs would improve the power of the resultant analysis. Blinding of the person delivering the induction agent and the person assessing the quality of induction and recovery would assist in removing bias.

Importantly, the results of this study should not be extrapolated to other groups of patients anaesthetised in clinical practice. Further studies remain to be undertaken within the clinical context to examine the benefits of the newer inhalants in such areas as paediatric patients, geriatric patients, and patients compromised by systemic disease or trauma. Recovery from anaesthesia may be significantly improved using the newer agents when patients are anaesthetised for considerably longer than the mean 70min occurring in the current study.

The variance between these results and those previously reported is likely to be primarily due to the clinical environment. A dog handled by strangers in an unusual environment will respond to the induction agent somewhat differently to a dog acclimated to its surroundings, the staff, and the procedure. In the clinical situation, the former case is the usual. In an analysis of the differences between induction agents, these unpredictable responses may be considered confounding factors, as the influence of the specific agent becomes harder to discern. However, it is difficult to recommend the use of a particular agent in the clinical situation if the theoretical advantages of that agent can not be demonstrated in the clinical environment.

Chapter 5: References

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