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.

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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.