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Clinical effects of midazolam or lidocaine co-induction with a propofol target-controlled infusion (TCI) in dogs

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Abstract

Objective To evaluate the propofol requirement, cardiovascular and respiratory variables using midazolam or lidocaine with a propofol target-controlled infusion (PTCI) for induction of anaesthesia in healthy dogs.

Study design Prospective, randomized, controlled blinded clinical trial.


Methods Thirty minutes after premedication with acepromazine (0.03 mg kg\(^{-1}\)) and morphine (0.2 mg kg\(^{-1}\)), PTCI was started and maintained at a plasma target concentration of 1 µg mL\(^{-1}\). Three minutes later, dogs \((n = 20\) per group) received either 5 mL 0.9% sodium chloride (SG), 2 mg kg\(^{-1}\) of lidocaine (LG) or 0.2 mg kg\(^{-1}\) of midazolam (MG) intravenously (IV) as a co-induction agent. Two minutes later, suitability for endotracheal intubation was assessed. If intubation was not possible, the propofol target was increased
by 0.5 µg mL\(^{-1}\) every 60 seconds until it was successfully achieved. Heart rate (HR), respiratory rate (\(f_R\)), and oscillometric systolic arterial pressure (SAP), mean arterial pressure (MAP) and diastolic arterial pressure (DAP) were recorded immediately prior to commencing PTCI (B0), prior to intubation (BI), immediately after (T0), and at 3 (T3) and 5 (T5) minutes post-intubation. End-tidal partial pressures of carbon dioxide (\(P_{E^\prime}CO_2\)) were recorded at T0, T3 and T5. The occurrence of excitement at any time point was noted.

**Results** The median (range) propofol target concentration for endotracheal intubation was significantly lower in MG, 1.5 (1.0 - 4.0) µg mL\(^{-1}\) compared with LG, 2.5 (1.5 - 4.5) µg mL\(^{-1}\) or SG, 3.0 (2.0 - 5.0) µg mL\(^{-1}\). Heart rate, MAP, \(f_R\) and \(P_{E^\prime}CO_2\) were similar in the three groups at all time points. No excitement was reported in any dog.

**Conclusions and clinical relevance** Midazolam, but not lidocaine, provided a significant reduction in PTCI requirement for induction of anaesthesia thereby allowing successful intubation. However, cardiovascular and respiratory effects were not different between the groups.

**Keywords** co-induction, lidocaine, midazolam, propofol, target-controlled infusion.

**Introduction**

Propofol is widely used for induction of general anaesthesia in dogs but commonly produces both cardiovascular and respiratory depression (Nakaigawa et al. 1995; Muir & Gadawski 1998). While the latter can be managed using intermittent positive pressure ventilation, the cardiovascular effects, primarily vasodilatation at the usual clinical doses, are more clinically challenging (Goodchild & Serrao 1989). Although these effects are
generally well tolerated by healthy dogs, those with any degree of pre-existing cardiovascular compromise may be unable to compensate for these changes.

Propofol target-controlled infusion (PTCI) has been used for induction and maintenance of anaesthesia in dogs (Beths et al. 2001; Musk et al. 2005). This technique employs a software-controlled syringe pump that delivers propofol as a variable rate infusion to achieve and maintain a user-selected plasma target concentration, which is based on population pharmacokinetic parameters and patient factors including body weight. The predicted plasma target concentration of propofol for induction of general anaesthesia in dogs ranges from 3 to 6 µg mL\(^{-1}\) (Beths et al. 2001; Musk et al. 2005; Beier et al. 2009). This range is similar to that reported in man (White & Kenny 1990). One recognized benefit of PTCI for induction of anaesthesia is that this technique allows a gradual increase in the plasma concentration as compared with manually controlled infusion techniques (Struys et al. 1997). This may potentially result in less cardiovascular depression (Stokes & Hutton 1991).

Using a ‘co-induction’ technique can also potentially lessen the cardiovascular-depressant effects of propofol. Co-induction refers to the administration of a sedative, anaesthetic or analgesic drug along with the main hypnotic agent to reduce the dose of induction agent required (Armein et al. 1995). To achieve a beneficial effect from co-induction, the drug selected should not only have a hypnotic dose-sparing action but must have minimal cardiovascular depressant effects of its own.

In human anaesthesia, the use of midazolam as a co-induction agent with propofol is well documented but the results in studies have been conflicting. Oxorn et al. (1997) did not observe any significant effect of midazolam on the propofol requirement whereas others have demonstrated an approximate 50% reduction in propofol dose for induction of
anaesthesia if midazolam is given up to 10 minutes prior to propofol administration (Short & Chui 1991; Ong et al. 2000). Premedication with midazolam also increased the number of human patients achieving successful induction of general anaesthesia with a fixed low target of PTCI without major cardiovascular effects (Tzabar et al. 1996). In dogs, however, midazolam administered as an intramuscular (IM) premedication or intravenous (IV) co-induction agent, at doses of 0.1 and 0.2 mg kg\(^{-1}\) respectively, resulted in excitement and only a mild reduction in propofol requirement for induction of anaesthesia (Stegmann & Bester 2001; Covey-Crump & Murison 2008; Hopkins et al. 2014). These outcomes can be improved if midazolam is administered soon after a sub-hypnotic bolus of propofol (Sanchez et al. 2013). Currently, there are no published reports of the effects of midazolam on either the plasma propofol target required or its cardiovascular and respiratory effects when used as a co-induction agent with PTCI in dogs.

In man, co-induction with lidocaine results in a lower dose requirement of propofol for induction of anaesthesia thus limiting the associated cardiovascular depression (Senturk et al. 2002; Kelsaka et al. 2011; Yang et al. 2013). In contrast, in dogs, there does not appear to be a sparing effect when lidocaine is administered immediately prior to propofol induction of anaesthesia (Braun et al. 2007). The effects of co-induction with lidocaine on PTCI in dogs, however, have not been investigated.

The aims of the present study were to evaluate if co-induction with midazolam or lidocaine could reduce the requirement of PTCI in healthy dogs for induction of general anaesthesia, and to investigate the effects of each drug combination on cardio-respiratory variables.

**Materials and methods**
The present clinical study was approved by the Ethics Committee of the School of Veterinary Medicine, University of Glasgow. The Veterinary Medicines Directorate approved the use of morphine, lidocaine and midazolam. Informed client consent was not obtained because the present study was started prior to becoming a requirement for publication.

*Animals*

Sixty client-owned dogs of various breeds, scheduled for elective surgical procedures at the Small Animal Hospital, University of Glasgow, were enrolled in the study. The dogs were considered eligible for inclusion if categorized as American Society of Anesthesiologists (ASA) physical status I or II, based on history and physical examination. Haematology and serum biochemistry were carried out in some but not all dogs depending on the preference of the individual clinician referring the dog for anaesthesia. Dogs were not considered eligible if brachycephalic, significantly overweight, younger than 6 months or older than 8 years of age, receiving opioid analgesic medication or with a history of vomiting/regurgitation or respiratory obstruction.

*Study protocol*

For the purpose of the study, dogs were randomly assigned to one of three groups prior to premedication \((n = 20\) for each group) using a computer-generated random numbers list: saline group (SG), lidocaine group (LG) and midazolam group (MG). Dogs in SG received a total volume of 5 mL of 0.9% sodium chloride \((\text{Vetivex; Dechra Veterinary Products, UK})\) IV. Dogs in LG received 2 mg kg\(^{-1}\) of lidocaine 2% \((\text{Lidocaine hydrochloride injection 2%; Hameln Pharmaceuticals Ltd, UK})\) IV whereas those in MG received 0.2 mg kg\(^{-1}\) of midazolam \((\text{Hypnovel, 10 mg 2 mL\(^{-1}\); Roche Products Ltd, UK})\) IV. In the last two groups,
the co-induction drug was diluted to a total volume of 5 mL with 0.9% sodium chloride to facilitate blinding.

Food, but not water, was withheld for 8 to 12 hours prior to premedication. Premedication was carried out using acepromazine (ACP Injection 2 mg mL\(^{-1}\); Novartis Animal Health Ltd, UK), 0.03 mg kg\(^{-1}\) up to a maximum of 1 mg, and morphine (Morphine Sulphate injection, 10 mg mL\(^{-1}\); Martindale Pharmaceuticals, UK), 0.2 mg kg\(^{-1}\), mixed in the same syringe and injected IM into the epaxial muscles of the neck. Thirty minutes after administration of premedication, the level of sedation was scored (Appendix 1) and the dogs were moved into a quiet induction room to minimize stimulation throughout the study period. An intravenous cannula (Biovalve PTFE; Vygon, France) was placed into a cephalic vein.

Dogs were positioned in sternal recumbency for the entire duration of the data collection and connected to an electrocardiograph (Mindray PM-8000Vet, Shenzhen Mindray Bio-Medical Electronics Co, Ltd, China) and an oscillometric blood pressure monitor (Cardell Veterinary Monitor 9401 BP, Sharn Veterinary Inc., FL, USA).

Pre-oxygenation via a facemask connected to a coaxial Bain breathing system (Intersurgical Ltd, UK) was commenced at a flow rate of 200 mL kg\(^{-1}\) minute\(^{-1}\) for at least 3 minutes before induction of general anaesthesia and was continued until successful intubation. Propofol TCI was administered via a syringe driver (Graseby 3500 Anaesthesia Pump; SIMS Graseby Ltd, UK) incorporating a ‘PK-Fusor for propofol 10 mg mL\(^{-1}\) in dogs’ software. The age and body weight of the dog were entered into the device, and a propofol plasma target concentration of 1 µg mL\(^{-1}\) was selected. Propofol TCI was then started. At 3 minutes after attainment of the plasma target concentration, the co-induction drug (midazolam, lidocaine or saline) was administered IV over 30 seconds. Any reaction, for
example, patient excitement, was noted. Two minutes later, the dog was assessed to
determine if endotracheal intubation was possible by checking pre-established end points:
weakened palpebral reflex, rostromedial rotation of the eyeball, a reduction in jaw tone and
lack of tongue withdrawal. When these conditions were obtained, endotracheal intubation
was attempted. If these criteria were not met, the propofol plasma target concentration was
increased in a stepwise manner by 0.5 µg mL$^{-1}$ each 60 seconds, reassessing the dog at
each new target until successful endotracheal intubation was achieved. The required
propofol target concentration was recorded.

Heart rate, $f_R$, SAP, MAP and DAP were recorded just prior to commencing PTCI (B0),
prior to intubation (BI), immediately after (T0), and at 3 (T3) and 5 (T5) minutes post-
endotracheal intubation. To measure the blood pressure, an inflatable cuff was applied to
the base of the tail, using a cuff width of approximately 40% of the circumference. The
blood pressure was measured four times: the first measurement was discarded and the
following three measurements were averaged to maximize the accuracy of the readings.
The end-tidal partial pressure of CO$_2$ ($P_{E\cdot CO_2}$) (Nellcor NPB-70; Mallinckrodt,
Netherland), and arterial haemoglobin oxygen saturation (SpO$_2$) (Nonin Model 9847V;
Nonin Medial, Inc., MN, USA) were also recorded immediately after (T0), and at 3 (T3)
and at 5 (T5) minutes post-intubation. If post-induction apnoea (defined as the absence of
spontaneous respiratory effort for at least 60 seconds) occurred, manual ventilation at a rate
of 2 breaths per minute was initiated until spontaneous ventilation resumed. The adjustable
pressure-limiting valve of the Bain breathing system was closed and the rebreathing bag
was manually squeezed to achieve a maximum peak inspiratory pressure of 20 cmH$_2$O
during inspiration.
Once the data collection was completed, the PTCI was discontinued and general anaesthesia was maintained according to the requirement of the procedure the dog was undergoing.

**Statistical analysis**

Power analysis, based on data derived from a pilot study with 18 dogs in total, indicated that a sample size of at least 18 dogs per group would detect a clinically significant difference of 0.5 µg mL\(^{-1}\) for the predicted plasma target concentration of propofol for induction of anaesthesia with a power of 80%.

Variables were checked for normality by examining box plots and histograms. Either the mean or median values were used for statistical comparison of data between the groups. Propofol target concentration data were analysed using Kruskal–Wallis and post-hoc Mann–Whitney tests. The age, body weight, HR, MAP, \(f_R\), \(P_{ECO_2}\) and SpO\(_2\) were analysed using t-tests and repeated measures analysis of variance (one-way and within a general linear model framework). Chi-squared tests were used to examine the association between categorical variables (sedation score, sex). All analyses were performed using Minitab 16 (Minitab Inc., UK). A p-value of < 0.05 was considered statistically significant.

**Results**

**Demographics**

Of the 60 dogs included in the study, 29 were male and 31 female, with a mean age of 48 ± 27 months and a mean body weight of 29 ± 9.7 kg. There were no differences between the three groups with respect to age, body weight or sedation score after premedication.

**Plasma target concentration of propofol**

The median (range) values of the plasma target concentrations of propofol for induction of anaesthesia were 1.5 (1.0–4.0) µg mL\(^{-1}\), 2.5 (1.5–4.5) µg mL\(^{-1}\) and 3.0 (2.0–5.0) µg mL\(^{-1}\) in
MG, LG and SG, respectively (Fig. 1). The propofol target concentration was statistically significantly lower in MG compared with LG ($p = 0.0022$) and SG ($p = 0.0001$). No significant difference in the propofol requirement was observed between LG and SG. The sedation score after premedication did not affect the target concentration of propofol required for successful intubation.

**Cardiovascular variables**

In the three groups, HR increased before intubation (BI) and after intubation (T0) compared with B0 values and decreased at 3 (T3) and 5 minutes (T5) after intubation (Fig. 2a). The HR was significantly affected by time ($p < 0.001$) and subject variability ($p < 0.001$) but not by the co-induction agent. There was no significant difference in the change in HR after intubation (T0) compared with before intubation (BI) between the three groups. The mean change in HR (95% CI) after intubation was +11.0 beats minute$^{-1}$ (6.7 to 15.5) in MG, +7.8 beats minute$^{-1}$ (0.2 to 15.4) in LG and +5.0 beats minute$^{-1}$ (−0.2 to 10.3) in SG.

In the three groups, the MAP increased before (BI) and after intubation (T0) compared with B0 values and decreased at 3 (T3) and 5 minutes (T5) after intubation (Fig. 2b). The mean arterial pressure was significantly affected by time ($p = 0.008$) and subject variability ($p < 0.001$) but not by the co-induction agent. There was no significant difference in the change in MAP after intubation (T0) compared with before intubation (BI) between the three groups. The mean change in MAP (95% CI) after intubation was +1.0 mmHg (−3.1 to 5.2) in MG, +6.0 mmHg (0.5 to 11.4) in LG and +2.3 mmHg (−1.7 to 6.2) in SG.

**Respiratory variables**

The respiratory rate was similar in the three groups at all time points. Values were lower after intubation (T0) and increased by the end of the data collection (T5) in all groups. Post-induction apnoea was not observed in any of the dogs. The values of $P_{E}$-CO$_2$ were similar in
the three groups at all time points. Recorded values were lower after intubation (T0) and increased by the end of the data collection (T5) in all groups (Table 1).

In all dogs, SpO₂ was always equal or greater than 98% at all time points. Values were similar in the three groups at all time points.

**Discussion**

The present study demonstrated that only co-induction with midazolam was associated with a significantly lower propofol plasma target concentration for successful endotracheal intubation in healthy dogs. In addition, the median target in dogs in the saline group agreed with previously reported findings for a similar premedication protocol but with a PTCI as the sole induction agent (Beths et al. 2001; Musk et al. 2005).

Propofol exerts its anaesthetic-hypnotic effect by potentiating GABAₐ receptor activity in the brain and spinal cord (Sanna et al. 1995). Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the central nervous system. Midazolam also enhances the affinity of GABAₐ receptors for GABA (Jensen & Lambert 1986); therefore, when midazolam is combined with propofol as premedication or as a co-induction agent, a synergistic interaction for hypnosis and immobility would be anticipated. This has been demonstrated in various studies in man where patients receiving midazolam as a co-induction agent required lower propofol doses for induction of anaesthesia (Short & Chui 1991; Wilder-Smith et al. 2001). Such an effect has not been seen in previous studies in dogs, where a high incidence of acute behavioural changes including excitement has been noted when midazolam was used either for premedication or as a co-induction agent with propofol (Stegmann & Bester 2001; Covey-Crump & Murison 2008). These behavioural changes may have affected subsequent propofol requirements, potentially offsetting any
hypnotic-sparing effect midazolam may produce in the absence of excitation. Covey-
Crump and Murison (2008) reported no decrease in the required propofol dose when
assessing midazolam co-induction. However, they reported results for the midazolam group
as a whole and did not look specifically at the propofol requirement relative to the
individual animal’s level of excitement.

Paradoxical excitation is rarely reported in man and its origin is unclear. One theory states
that the inhibitory action of benzodiazepines may cause a loss of cortical restraint in some
patients, leading to excitement (Paton 2002). Other authors hypothesize that it may be
correlated with central cholinergic effects, as it can be partially antagonized with
cholinesterase inhibitors such as physostigmine (Di Liberti et al. 1975). The serotonergic
system may also be involved when aggressive behaviour occurs (Senninger & Laxenaire
1995). In the present study, it was hypothesized that by administering a sub-hypnotic dose
of propofol at a plasma target concentration of 1 µg mL⁻¹ prior to administering midazolam,
we could potentially avoid any unwanted excitatory effects and achieve a reduction in the
total propofol requirements for induction of anaesthesia. This was confirmed by our results,
in that no dog exhibited excitement after administration of the co-induction drugs, and
significant propofol-sparing effects were demonstrated for midazolam. Similar findings
have been reported in recently published canine studies where administration of a small
bolus dose of propofol prior to midazolam co-induction resulted in a reduced propofol
requirement for induction of anaesthesia; however, the excitatory effects, although reduced,
were not eliminated completely using this technique (Sanchez et al. 2013; Robinson &
Borer-Weir 2013; Hopkins et al. 2014). In this present study, we demonstrated the effect of
midazolam in reducing the propofol target concentration required for induction of
anaesthesia in dogs, when a TCI system was used, and the ability of this technique to minimize the incidence of any excitatory effects.

Unlike midazolam, lidocaine did not reduce propofol requirements for induction of anaesthesia in the present study, which is in agreement with the findings of Braun et al. (2007). The absence of a propofol-sparing effect of lidocaine in dogs is perhaps surprising because a reduction in the isoflurane and sevoflurane minimum alveolar concentration is demonstrated in this species when lidocaine is given as a constant rate infusion with inhaled anaesthetic agents (Muir et al. 2003; Valverde et al. 2004; Matsubara et al. 2009). In man, in contrast, IV or IM administration of lidocaine reduces the induction dose of propofol (Senturk et al. 2002; Kelsaka et al. 2011). In addition, humans receiving PTCI with a lidocaine infusion for maintenance of general anaesthesia had a reduction in the bi-spectral index-guided requirements for propofol was but this effect was only observed during surgical stimulation (Hans et al. 2010). As lidocaine has anti-nociceptive properties, it may produce anaesthetic sparing effects only during noxious stimulation. This could explain why no reduction in the propofol target was observed with lidocaine co-induction in the present study.

In the present study, the cardiovascular variables (the mean HR and MAP) were similar between the three groups of dogs at all time points. Induction of anaesthesia with high doses of propofol generally produces vasodilatation and direct myocardial depression in dogs (Ismail et al. 1992). However, despite the resulting decrease in cardiac output and arterial blood pressure, propofol anaesthesia is classically characterized by a relatively low HR when compared with other hypnotics, such as thiopentone or alfaxalone (Quandt et al. 1998; Amengual et al. 2013). This effect has been explained by two different mechanisms. First, there is a central effect of ‘resetting’ the baroreflex response through vagotonic and/or...
sympatholytic effects of the drug (Cullen et al. 1987; Samain et al. 1989) and second a
peripheral effect of inhibition of the sympathetic nervous activity and decreased baroreflex
sensitivity (Sellgren et al. 1994, Chen et al. 2011).

Midazolam often causes a rise in HR in dogs when used as a co-induction agent in
conjunction with propofol (Covey-Crump & Murison 2008; Sanchez et al. 2013; Hopkins
et al. 2014). This increase in HR may occur as a result of excitation (Stegmann & Bester
2001); however, Sanchez et al. (2013) reported that, a sub-anaesthetic dose of propofol
given prior to midazolam reduced the incidence of paradoxical excitation but did not
prevent an increase in HR, making this cardiovascular effect more complex to explain fully.

In man, when midazolam is used in a similar manner, as a co-induction agent with
propofol, an increase in HR also occurs when compared with the use of propofol alone.
This is explained by the sparing effect of midazolam on propofol induction dose preserving
baroreflex activity in response to a decrease in blood pressure (Win et al. 2007). The
changes in HR and MAP observed in the midazolam group, in this study were no different
to those seen in the saline group. Midazolam is generally considered to have minimal
effects on cardiovascular function; however, at the dose used in the present study, slight
vasodilatation may occur in dogs (Jones et al. 1979). Although midazolam significantly
decreased propofol induction requirements, it did not produce any greater preservation of
MAP than propofol alone. This may suggest that midazolam itself contributed to a decrease
in MAP and, therefore, there would appear to be no valid reason to consider midazolam a
suitable co-induction agent with propofol in healthy dogs.

Similar to midazolam, lidocaine co-induction did not produce cardiovascular effects that
differed from propofol alone, with no significant differences in the mean HR or MAP at
any time point between dogs in the LG and SG groups. Laryngoscopy, stimulation of the
upper airways and endotracheal intubation are associated with haemodynamic changes that can result in increased HR and MAP (Halevy et al. 2003). In humans, IV lidocaine has been shown to blunt this response (Qi et al. 2013); consequently, it might be anticipated that HR and MAP would have been lower in LG compared with SG dogs after endotracheal intubation but this was not observed. This would suggest that lidocaine does not obtund the pressor response to endotracheal intubation in dogs to the same extent as it does in humans. A previous study similarly demonstrated no benefit on SAP and HR variables in dogs when lidocaine was injected just prior to propofol induction (Jolliffe et al. 2007). It was also possible, however, that any pressor response to intubation in the dogs in the present study was too transient to be detected by an oscillometric blood pressure system. These findings may support that administration of propofol to effect using a PTCI is already a technique with clinically acceptable haemodynamic stability.

In the present study, the mean $f_R$ and $P_{E CO_2}$ were similar in the three groups at all time points and none of the dogs developed post-induction apnoea (PIA). A rapid manual bolus injection of propofol for induction of anaesthesia can cause respiratory depression and apnoea in healthy dogs (Muir & Gadawski 1993; Amengual et al. 2013). Previous studies have demonstrated a high incidence of PIA depending on the speed of administration of the drug. A rate of occurrence of PIA of 75% occurred when propofol was injected over 30–60 seconds (Bufalari et al. 1997) and 60% when propofol was administered over 20–30 seconds (Murison 2001). Musk et al. (2005) showed that the incidence of PIA could be reduced to 30–45% when propofol is administered slowly by TCI. In this study, our PTCI technique eliminated the occurrence of PIA. This may have been the result of a slow incremental increase of a propofol target concentration and repeated assessment of suitability for intubation. The use of midazolam as a co-induction agent did not increase the
incidence of PIA. This is in contrast to other studies where PIA appeared to be a problem in any of the groups (Covey-Crump & Murison 2008; Sanchez et al. 2013; Hopkins et al. 2014).

There are some limitations of this present study. First, all of the dogs were healthy patients undergoing elective procedures. Co-induction techniques may be more beneficial in non-healthy dogs such as those with a degree of pre-existing cardiovascular compromise. In addition, the use of non-invasive arterial blood pressure monitoring may not be accurate in detecting rapid changes in blood pressure. Given that this was a clinical study, it would not have been possible from an ethical point of view to perform an invasive monitoring technique, given the ASA physical status of the dogs and procedures being undertaken.

Conclusions

Co-induction with midazolam, but not lidocaine, reduced the propofol requirements for endotracheal intubation in healthy dogs when using a TCI system. Despite a significant reduction in propofol plasma target concentration in the midazolam group, no haemodynamic benefits were observed after endotracheal intubation. However, further studies are needed to evaluate the effects of this co-induction technique in non-healthy dogs.

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