Dose requirement and cardiopulmonary effects of diluted and undiluted propofol for induction of anaesthesia in dogs

Running head: Diluted propofol for anaesthetic induction in dogs

31-03-2020, Utrecht

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Word Count: 1996 words

Abstract 300 words

Objective: To compare anaesthetic induction in healthy dogs using propofol (10 mg mL^{-1}) and diluted propofol (5 mg mL^{-1}).

Study design: Prospective, randomized, blinded, clinical study.

Animals: Thirty healthy dogs (13 males/17 females), aged 7 - 183 months and weighing between 3.6 - 44.4 Kg.

Methods: Following intramuscular sedation (acepromazine 0.02 mg Kg^{-1} and methadone 0.2 mg Kg^{-1}), propofol (10 mg mL^{-1}) (UP) or diluted propofol (5 mg mL^{-1}) (DP) was administered intravenously by an anaesthetist unaware of the treatment group until tracheal intubation was possible. Sedation, intubation and induction quality were scored. Baseline and postinduction pulse rate (PR), respiratory rate (f_R) and systolic (SAP), mean (MAP) and diastolic (DAP) blood pressure were measured and compared. Time to first breath (TTFB) and induction dose were recorded. Data was analysed for normality and Mann-Whitney U or Student's t tests were performed where adequate. The level of significance was set at $p \leq 0.05$. Data was presented as mean ± standard deviation or median (range) as appropriate.

Results: The dose of propofol administered to achieve induction was lower in the DP group (2.64 ± 0.47 mg Kg^{-1}) than in the UP group (3.48 ± 1.17 mg Kg^{-1}) ($p = 0.02241$). No significant difference was observed in baseline and postinduction PR, SAP, MAP, DAP and f_R between groups. Difference between baseline and postinduction of the same parameters was not different between groups. TTFB was not different between groups. Sedation was similar between groups. Quality of tracheal intubation was better with UP 0 (0-1) than with DP 1 (0-2) ($p = 0.03585$), but overall quality of induction was similar between groups [UP 0 (0-1) and DP 0 (0-1), $p = 0.5497$].

Conclusion and clinical relevance: Diluting propofol reduced the dose required to induce anaesthesia, but did not significantly alter cardiorespiratory parameters associated to it.

Keywords

propofol; dog; induction of anaesthesia; dilution; dose; cardiorespiratory

Introduction

Several injectable drugs have previously been used to induce anaesthesia, but an ideal agent has still not been produced.

Propofol, a phenol-derivative anaesthetic agent, is commonly used for induction of anaesthesia due to its short duration and rapid action. It can exhibit some cardiorespiratory side effects (e.g. hypotension, hypoventilation and apnoea), but these are dose-dependent (Taylor et al. 1986; Amengual et al. 2013).

Due to its physicochemical properties, propofol requires time to reach the targeted receptors (Stokes et al. 1991). In humans, cats, and dogs, slower infusion rates of propofol have resulted in lower doses required to induce anaesthesia, and in less cardiorespiratory depression (Peacock et al. 1990; Bauquier et al. 2017; Bigby et al. 2017). The dilution of propofol may achieve a similar outcome without having to slow the induction rate. Additionally, it might be safer, as the dose can be titrated more accurately (especially in very small animals). However, to the authors knowledge, the use of diluted propofol and its effects during induction of anaesthesia has not been investigated in animals.

The aim of this study was to investigate the dose and cardiorespiratory effects of diluted propofol (DP) (5 mg mL^{-1}) for induction of anaesthesia in dogs. The secondary aim was to compare DP with the undiluted commercial presentation of propofol (UP) (10 mg mL^{-1}). Our first hypothesis was that the use of DP would result in a significant reduction in dose required to induce anaesthesia compared to UP. Our second hypothesis was that the use of DP would result in a significant reduction of cardiorespiratory side-effects compared to UP.

Material and methods

Animals

The study was approved by the University of Sydney Animal Research Authority (2019/1514). A total of 30 dogs (American Society of Anaesthesiologists (ASA) classification I or II) admitted to the University of Sydney Veterinary Teaching Hospital were recruited for this study. The dogs required general anaesthesia for various surgical or diagnostic procedure and full client consent was obtained before inclusion. The dogs that were not amenable to intravenous catheter placement following pre-anaesthetic sedation or the dogs that required more than the predetermined propofol dose for intubation were excluded from the study.

Anaesthetic technique and monitoring

The dogs were fasted for 8 to 12 hours prior to anaesthesia, but were allowed access to water until sedation was administered. This consisted of acepromazine 0.02 mg Kg^{-1} (ACP 2 mg mL^{-1}: Ceva Animal Health Pty Ltd, NSW, Australia) and 0.2 mg Kg^{-1} methadone (Methadone 10 mg mL^{-1} injection Ilium, Troy Laboratories Pty Ltd, NSW, Australia) administered intramuscularly. After at least 30 minutes, the degree of sedation was assessed and scored using a four-point scale from 0 to 3 (no sedation to profound sedation) (Covey-Crump & Murison, 2008). A venous catheter was placed into one of the cephalic veins following an aseptic technique and a suitable blood pressure cuff was placed over the mid antebrachium of the contralateral front limb. At 1,3 and 5 minutes after catheter placement, the systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), mean arterial blood pressure (MAP) and pulse rate (PR) were measured using oscillometry (Cardell Veterinary Monitor: Midmark

Corporation, Ohio, USA). Respiratory rate (f_R) was measured by counting the number of breaths in thirty seconds and timing by two. Finally, the dogs were preoxygenated using a flow of 1-2 L minute^{-1} 100% oxygen for five minutes.

Dogs were randomly allocated [based on an electronically generated list (https://studyrandomizer.com; Phase Locked Software, The Netherlands)] to receive either propofol 10 mg mL^{-1} (Provive 1%: AFT Pharmaceuticals, NSW, Australia) or propofol 5 mg mL^{-1} administered intravenously by a syringe-driver (Asena CC: Alaris Carefusion, Switzerland) at a rate of 0.2 mL Kg^{-1} minute^{-1}. The DP was prepared by diluting the commercially available propofol 50:50 in volume with saline (Sodium Chloride 0.9%: Baxter, NSW, Australia). The syringe-driver was checked for accuracy before the onset of this study. A dose of 4 mg Kg^{-1} of either DP or UP (depending of the group allocation) was calculated and drawn up in a suitable sized syringe, then additional induction agent was added to fill the syringe to its maximal capacity. The anaesthetist performing the inductions and taking the measurements was unaware of the concentration of propofol used (both solutions are indistinguishable). The induction solution was infused until ventro-medial eye rotation, jaw relaxation, and no reaction to tongue-base depression with the laryngoscope were observed. The syringe-driver was then stopped and the orotracheal intubation was performed by a final year veterinary student. After intubation, the endotracheal tube was connected to a circle breathing system and 100% oxygen was administered at a flow of 1-2 L min^{-1}.

The total volume of solution was recorded, and the quality of intubation was assessed using a four-point scale from 0 to 3 (smooth to very poor) (Covey-Crump & Murison 2008). The time to first spontaneous breath (TTFB) after intubation was measured in

seconds. Postinduction apnoea was defined in this study as no spontaneous breaths observed for 60 seconds. When dogs became apnoeic or whenever the arterial oxygen saturation (SpO_2) (Cardell Veterinary Monitor: Midmark Corporation, Ohio) dropped below 95%, a manual ventilation was provided every 15 seconds until they resumed spontaneous breathing. The TTFB in apnoeic animals was recorded as 60 seconds, but in in the case dogs required ventilation due to low $SpO_{2,}$ it was not included in the results. At 1, 3, and 5 minutes after endotracheal intubation SAP, DAP, MAP, PR and f_R were measured.

Finally, the induction quality was also scored using a four-point scale from 0 to 3 (smooth to very poor) (Covey-Crump & Murison 2008). Five minutes after endotracheal intubation and connection to the anaesthetic breathing system, the research protocol was considered completed.

Statistics

After performing a pilot study, a sample size of 30 dogs was estimated adequate to detect a 1 mg Kg^{-1} difference in the induction dose using a 90% power and a 0.05 alpha value.

For each dog, the average SAP, MAP, DAP, PR and f_R for both before and after induction were calculated and compared between both groups (UP and DP). Furthermore, the difference between baseline and postanaesthetic induction of the same parameters was calculated for each dog and compared between groups. TTFB was compared between groups. Induction dose (mg Kg^{-1}) was calculated by multiplying the induction volume per the solution concentration and dividing the result by the bodyweight. The data were tested for normality using a Shapiro-Wilk

test and the groups were compared using unpaired Student's t or Mann-Whitney U tests. A X^2 test was used to compare sex and ASA-status between groups. Values of $p < 0.05$ were considered significant. Results are presented as mean ± standard deviation or median (range) as appropriate. Statistical analysis was carried out using R V.3.3.2 Mac OS (The R Foundation for Statistical Computing, http://www.R-project.org, Austria).

Results

Fifteen dogs were enrolled in each group. One dog in the UP group was excluded, as intubation was not possible with the predetermined propofol volume. One dog in the DP group regurgitated during intubation, requiring immediate intervention from the attending anaesthetist and therefore was excluded. In both cases, the pre-induction parameters were included in the results.

Dogs were between 7 and 183 months of age and weighing between 3.6 and 44.4 Kg. Dogs were similar in signalment and groups were not different in terms of ASA classification (Table 1). There was also no difference in sedation scores between groups [UP 1 (1-2) and DP 1 (1-3)) p = 0.9626].

The volume of induction agent administered to achieve induction was higher with DP (0.53 ± 0.09 mL Kg^{-1}) than with UP (0.42 ± 0.07 mL Kg^{-1}) (p = 0.001964). The dose of propofol administered to achieve induction was lower in the DP group (2.64 ± 0.47 mg Kg^{-1}) than in the UP group (3.48 ± 1.17 mg Kg^{-1}) (p = 0.02241).

No significant difference was observed in PR, SAP, MAP, DAP and f_R between groups measured at baseline and postanaesthetic induction. Furthermore, the difference between baseline and postanaesthetic induction of the same parameters was

not different between groups. TTFB was slightly shorter in the DP group, but this was not significant (Table 2). Two dogs in the UP group showed postinduction apnoea of more than 60 seconds. One dog In the DP group required ventilation as SpO_2 dropped below 95%.

Quality of tracheal intubation was better with UP 0 (0-1) than with DP 1 (0-2) ($p = 0.03585$), but overall quality of induction was similar between groups [UP 0 (0-1) and DP 0 (0-1), $p = 0.5497$].

Discussion

The aim of this study was to investigate the dosing and cardiorespiratory effects of DP (5 mg mL^{-1}) for induction of anaesthesia in dogs. Furthermore, to compare these outcomes with UP (10 mg mL^{-1}). This study showed that the use of DP resulted in a significant reduction in the dose required to induce anaesthesia compared to UP.

Bigby et al. (2017) used a rate of 0.1 mL Kg^{-1} $minute^{-1}$ of UP to assess the effect of a slow rate of administration in the induction dose. That rate of administration in mg Kg^{-1} $minute^{-1}$ was very similar to the one used in our study (administering DP at 0.2 mL Kg^{-1} $minute^{-1}$). However, the dose reported by Bigby et al. (2017) (1.8 ± 0.6 mg Kg^{-1}) is lower than the dose reported in this study (2.64 ± 0.47 mg Kg^{-1}). This difference in dose might be related to a more profound level of sedation reported by Bigby et al (2017), but the use of a different scale makes a direct comparison difficult. However, this profound sedation was likely and directly attributable to the use of a higher dose of methadone (0.5 mg Kg^{-1}) and dexmedetomidine (5 µg Kg^{-1}) as sedation instead of methadone (0.2 mg Kg^{-1}) and acepromazine (0.02 mg Kg^{-1}).

Due to the pharmacokinetic properties of propofol, time is required to reach the receptors in the brain (Stokes et al. 1991). Therefore, a diluted concentration should avoid overshooting and reduce the amount of propofol required to induce anaesthesia. In consequence, a reduction of cardiopulmonary side effects should be expected. Comparable to former studies (Martinez-Taboada F & Leece 2014; Bigby et al. 2017), a decrease in f_R was recorded following propofol induction. However, panting was a common feature in both groups before induction and the decrease in f_R was similar in both groups. This study shows a slightly shorter, but not significant, TTFB when DP was used [11 (1-40) seconds]. This was similar to the time observed by Bigby et al. (2017) (10 ± 18 seconds) following slow administration of propofol. Previous research in dogs has shown dose-dependent cardiovascular depression following administration of propofol (Goodchild et al. 1989). In this study, despite administering different doses, a similar small decrease in blood pressure and increase in PR was seen in both groups. Possibly, meaningful dose-dependent cardiovascular depression only occurs at higher doses of propofol than the ones used here.

Quality of tracheal intubation was better with UP than with DP ($p = 0.03585$). It is possible that anaesthesia was slightly lighter after administration of DP. Nevertheless, intubation quality was acceptable in both groups and overall quality of induction was similar between groups.

There are several limitations in this study. Firstly, it would have been more accurate to measure respiratory depression using end-tidal CO_2 and spirometry rather than only apnoea and f_R. Secondly, counting of the TTFB was started after the intubation was completed by a final year veterinary student and some intubations were fairly time-consuming. It is likely that this variability impacted similarly both groups. Finally,

only non-invasive monitoring techniques were used and they are intrinsically inaccurate, especially detecting small changes. However, one may argue the clinical relevance of such small differences.

In conclusion, diluting propofol reduced the dose required to induce anaesthesia. Therefore, it results in a decrease in cost and more accurate administration. No significant differences were found in the cardiopulmonary and quality characteristics of the induction. Further research is required to investigate whether different degrees of dilution have similar effects.

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Table 1 Patients' signalment and studied parameters: values of pulse rate (PR), respiratory rate (f_R), systolic (SAP), mean (MAP) and diastolic (DAP) pressure at baseline (B) and postanaesthetic induction (P). Differences between postanaesthetic induction and baseline were calculated (P-B). Positive values indicate an increase of the parameter after induction, whereas negative values are equivalent to a depression of the parameter after induction. The time from tracheal intubation to first breath (TTFB) were also measured and compared between groups.

	Undiluted propofol	**Diluted propofol**	**P-value**
Signalment			
Sex (males/females)	5/10	8/7	0.269
Age (months)	87 ± 49	99 ± 41	0.445
Weight (Kg)	20.6 (5.0 – 37.0)	17.2 (3.6 – 44.4)	0.420
BCS (1 – 9)	5/9 (4/8 – 8/9)	5/9 (3/9 – 8/9)	0.983
ASA distribution (I/II)	9/6	6/9	0.273
Studied parameters			
PR_B (pulses min^{-1})	90 ± 26	84 ± 25	0.488
PR_P (pulses min^{-1})	92 ± 28	91 ± 29	0.887
PR_{P-B} (pulses min^{-1})	4 ± 26	10 ± 20	0.464

$f_{R\,B}$ (breaths min^{-1})	54 (15 – 209)	55 (12 – 277)	0.244
$f_{R\,P}$ (breaths min^{-1})	14 ± 8	19 ± 8	0.129
$f_{R\,P\text{-}B}$ (breaths min^{-1})	-29 (-113 – 4)	-39 (-256 – 17)	0.395
SAP_B (mmHg)	129 ± 18	129 ± 21	0.914
SAP_P (mmHg)	104 (83 – 124)	118 (83 – 167)	0.086
$SAP_{P\text{-}B}$ (mmHg)	-21 ± 17	-12 ± 18	0.177
MAP_B (mmHg)	92 ± 18	94 ± 15	0.692
MAP_P (mmHg)	75 ± 14	85 ± 18	0.110
$MAP_{P\text{-}B}$ (mmHg)	-14 ± 18	-9 ± 12	0.420
DAP_B (mmHg)	73 ± 15	78 ± 15	0.318
DAP_P (mmHg)	61 (44 – 90)	64 (46 – 100)	0.872
$DAP_{P\text{-}B}$ (mmHg)	-9 ± 17	-15 ± 12	0.350
TTFB (seconds)	23 (1 – 60)	11 (1 – 40)	0.145