RESEARCH PAPER

Comparison of propofol with ketofol, a propofol-ketamine admixture, for induction of anaesthesia in healthy dogs

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Abstract

Objective To compare anaesthetic induction in healthy dogs using propofol or ketofol (a propofol-ketamine mixture).

Study design Prospective, randomized, controlled, ‘blinded’ study.

Animals Seventy healthy dogs (33 males and 37 females), aged 6–157 months and weighing 4–48 kg.

Methods Following premedication, either propofol (10 mg mL−1) or ketofol (9 mg propofol and 9 mg ketamine mL−1) was titrated intravenously until laryngoscopy and tracheal intubation were possible. Pulse rate (PR), respiratory rate (fR) and arterial blood pressure (ABP) were compared to post-premedication values and time to first breath (TTFB) recorded. Sedation quality, tracheal intubation and anaesthetic induction were scored by an observer who was unaware of treatment group. Mann–Whitney or t-tests were performed and significance set at p ≤ 0.05.

Results Induction mixture volume (mean ± SD) was lower for ketofol (0.2 ± 0.1 mL kg−1) than propofol (0.4 ± 0.1 mL kg−1) (p < 0.001). PR increased following ketofol (by 35 ± 20 beats minute−1) but not consistently following propofol (4 ± 16 beats minute−1) (p < 0.001). Ketofol administration was associated with a higher mean arterial blood pressure (MAP) (82 ± 10 mmHg) than propofol (77 ± 11) (p = 0.05). TTFB was similar, but ketofol use resulted in a greater decrease in fR (median (range): ketofol −32 (−158 to 0) propofol −24 (−187 to 2) breaths minute−1) (p < 0.001). Sedation was similar between groups. Tracheal intubation and induction qualities were better with ketofol than propofol (p = 0.04 and 0.02 respectively).

Conclusion and clinical relevance Induction of anaesthesia with ketofol resulted in higher PR and MAP than when propofol was used, but lower fR. Quality of induction and tracheal intubation were consistently good with ketofol, but more variable when using propofol.

Keywords dog, induction of anaesthesia, ketamine, ketofol, propofol.

Introduction

Propofol is widely used for induction of anaesthesia in dogs. It is a phenol-derivate sedative-hypnotic agent with rapid onset and short duration of action after a single bolus, which is followed by a smooth recovery. However, it is also associated with cardio-pulmonary depression (Short & Bufalari 1999), pain at induction [especially when micro-emulsion
formulations are used (Michou et al. 2012), and excitation following induction of anaesthesia characterised by muscle twitching, panting, padding, limb rigidity and opisthotonus (Davies & Hall 1991).

Ketamine is a phencyclidine derivate with sedative, anaesthetic and analgesic effects produced by N-methyl-D-aspartate receptor antagonism. The cardiovascular effects of ketamine are a direct depression of myocardial contractility (Pagel et al. 1992; Gelissen et al. 1996), usually masked by stimulation of sympathetic efferent activity, which increases heart rate and arterial blood pressure (Wong & Jenkins 1974).

Coadministration of ketamine and propofol, administered using separate syringes, has been successfully used with the intention of counteracting the unwanted effects of these drugs. In dogs, the decrease in heart rate occurring at anaesthetic induction was smaller when ketamine and propofol were administered (propofol and ketamine in separate syringes) than when propofol was given alone (Lerche & Nolan 2000) and similar findings were also observed in humans (Hui et al. 1995). Combining both drugs in a single syringe aims to simplify drug administration.

The mixture of propofol and a low dose of ketamine (ketofol) in the same syringe has been studied, particularly as continuous intravenous (IV) infusions for sedation and analgesia, both in healthy volunteers (Morse et al. 2003) and clinical patients in the emergency department (Willman & Andolfatto 2007; Andolfatto & Willman 2010; Phillips et al. 2010; Da Silva et al. 2011). The combination of these drugs sought the haemodynamic stability observed when given separately, with the convenience of managing only a single infusion. In managing the clinical data reported, the physical and chemical stability of ketamine: propofol combinations in 1:1 and 3:7 (mg) ratios has been demonstrated (Donnelly et al. 2008). Ketofol has received interest in veterinary anaesthesia, especially in feline patients. Ravasio et al. (2012) documented the use of ketofol infusion for ovariectomy in cats and Zonca et al. (2012) reported the pharmacokinetics of ketofol in cats after induction of anaesthesia and 25 minute constant rate infusion. To date, there is no information regarding the use of 1:1 propofol/ketamine admixture in dogs for induction of anaesthesia and its haemodynamic characteristics.

This study aimed to compare the cardiorespiratory variables and induction characteristics of dogs anaesthetized with either propofol or a propofol-ketamine admixture.

**Materials and methods**

The study was approved by the institutional ethics committee and the Veterinary Medicines Directorate (VMD) (animal test certificate number ATC-S-026), and informed owner consent was obtained.

Seventy dogs requiring general anaesthesia for various diagnostic and surgical procedures were included in the study. All the animals were assigned to American Society of Anesthesiologists (ASA) categories I or II on the basis of a thorough physical examination performed by the main investigator (FMT). Exclusion criteria were animals in ASA categories III to V, pregnant or lactating bitches, anaesthetic duration shorter than one hour and any case where it was felt the use of one or more of the drugs described in the protocol was contraindicated.

Dogs were fasted for 12 hours prior to induction of anaesthesia. Water was available until pre-anaesthetic medication was administered. This medication consisted of 0.02 mg kg\(^{-1}\) acepromazine (ACP injection 2 mg ml\(^{-1}\), Novartis Animal Health, UK) and 0.2 mg kg\(^{-1}\) methadone (Physeptone injection, methadone 1%, Martindale Laboratories, UK) administered by a single intramuscular injection in the lumbar epaxial muscles.

Thirty minutes after premedication, sedation was scored using a four point scale (0 = no sedation to 3 = profound sedation) as described by Murison (2001) (Appendix S1). An 18 or 20 gauge catheter (Jelco, Smith Medical International Ltd., UK) was inserted into a cephalic vein. A suitable blood pressure cuff (Critikon Soft-cuf, GE Healthcare, UK) (cuff width/metatarsal circumference ratio of 0.4) was placed over the dorsopedal artery for oscillometric blood pressure monitoring (Beneview T5, Shenzhen Mindray Bio-Medical Electronics Co, China). The arterial blood pressure was measured 1, 3 and 5 minutes after catheter placement. At these time points, pulse rate (PR) and breathing rate (f\(_{R}\)) were also recorded.

Dogs were randomly allocated to receive either propofol (Propoflo, Abbott, UK) or ketofol (1:1 mixture of approximately 9 mg ml\(^{-1}\) propofol and 9 mg ml\(^{-1}\) ketamine). This admixture was made by aseptically adding 200 mg of ketamine (Narketan 10, Vetoquinol, UK) to a 200 mg vial of propofol (Propoflo, Abbott, UK). Each vial of ketofol was kept for a maximum of 12 hours. A volume equivalent to
0.5 mL kg\(^{-1}\) of the specific induction agent (depending on group allocation) was calculated and then rounded to the nearest full commercial syringe for every dog (e.g. for a 5 kg patient, the calculated dose would be 2.5 mL and a full 5 mL was then drawn up). Syringes were not covered, as both aliquots are white; but they were labelled as ‘induction’.

The same anaesthetist (FMT), who was unaware of the treatment group, performed each anaesthetic induction. The induction agent was infused IV at an approximate rate of 0.2 mL kg\(^{-1}\) minute\(^{-1}\) until the patient showed ventro-medial eye rotation and jaw relaxation, and there was no reaction to tongue-base depression with a laryngoscope. Intravenous administration of the induction aliquot was performed by hand injection. The total volume injected was recorded and quality of intubation was assessed using the classification previously described by Covey-Crump & Murison (2008) (Supporting information Appendix S1). The endotracheal tube was then connected to a rebreathing circle system delivering a flow of 2 L minute\(^{-1}\) of 100% oxygen.

Pulse oximetry was used to monitor haemoglobin oxygen saturation (SpO\(_2\)) and PR and capnography was used for f\(_R\) monitoring (Beneview T5, Shenzhen Mindray Bio-Medical Electronics Co, China). The time (seconds) from tracheal intubation to the first spontaneous breath (TTFB) of the patient was measured using a stopwatch and then recorded. One manual ventilation was given if the SpO\(_2\) dropped below 92% or apnoea was noted for longer than 1 minute.

Arterial systolic, diastolic and mean blood pressure (SAP, DAP, MAP), PR and f\(_R\) were monitored at time points 1, 3 and 5 minutes post tracheal intubation. Dogs were anaesthetized by no other means than the induction agent/s during this time period. Induction characteristics and overall quality were assessed using a 4-point scale \([0 = \text{Smooth}\) (without excitement) to \(3 = \text{very poor}\) (severe excitement, muscle twitching, paddling of limbs, head movements and vocalization)]\) (Covey-Crump & Murison 2008) (Appendix S1). After the last measurement was taken, 5 minutes after tracheal intubation, the study was completed and anaesthesia proceeded as required. No further data was included in the present study (except in the case of relevant side effects attributable to the induction agent/s). In the event of inadequate depth of anaesthesia during the measuring period, a syringe with 2 mg kg\(^{-1}\) of propofol was always attached to the catheter T-connector with the clamp in the locked position.

This syringe was clearly labelled and it was segregated from the study drugs at all times.

After performing a pilot study, a sample size of 25 dogs per group was considered adequate to obtain a power of 90% to detect a difference of 10 mmHg mean BP with a \(p\) value of 0.05. Statistical analysis was performed using StatPlus for Mac OS X. The average PR, f\(_R\), SAP, MAP and DAP at baseline and post-induction were calculated for each dog and compared between groups. The difference between these pre and post-induction values was also calculated (PR\(_{p-B}\), f\(_R\)\(_{p-B}\), SAP\(_{p-B}\), MAP\(_{p-B}\), DAP\(_{p-B}\)) for every animal and compared between groups. TTFB, and quality of intubation and induction were compared between groups. Unpaired Student’s t tests and Mann-Whitney tests were used for normally and non-normally distributed data respectively. Level of significance was set at \(p \leq 0.05\). Data are presented as mean ± standard deviation or median (range) as appropriate.

Results

Signalment of dogs was similar between groups (Table 1). One dog in the propofol group was withdrawn from the study, as laryngoscopy was not possible after the volume of drug drawn up for it had been administered. This resulted in 34 dogs included in the propofol group and 35 in the ketofol group.

The volume of induction agent administered to achieve laryngoscopy was significantly lower in the ketofol group (0.2 ± 0.1 mL kg\(^{-1}\)) (1.8 ± 0.9 mg kg\(^{-1}\) of each propofol and ketamine) than in the propofol group (0.4 ± 0.1 mL kg\(^{-1}\)) (4 ± 1 mg kg\(^{-1}\)) \((p = 1.18 \times 10^{-7}\)). No difference was observed between groups in the cardiovascular parameters measured before induction of anaesthesia. PR post induction was signifi-

<table>
<thead>
<tr>
<th>Subject</th>
<th>Propofol</th>
<th>Ketofol</th>
</tr>
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<tbody>
<tr>
<td>Sex: Male/Female</td>
<td>22/12</td>
<td>15/20</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>20.4 ± 11.1</td>
<td>22.0 ± 12.7</td>
</tr>
<tr>
<td>Age (months)</td>
<td>29 (7–157)</td>
<td>36 (6–148)</td>
</tr>
<tr>
<td>American Society of Anesthesiologists (ASA) distribution (ASA I/II)</td>
<td>26/8</td>
<td>29/6</td>
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Table 1 Demographic distribution was not significantly different between groups
cantly higher in the ketofol group (111 ± 30) than in the propofol group (90 ± 21) (p < 0.001). When the post induction-baseline difference was calculated, a significant increase in PR was obtained in the ketofol group compared to the propofol group (35 ± 20 beats minute⁻¹ compared to 4 ± 16 beats minute⁻¹ respectively, p < 0.0001) (Table 2). Post induction SAP and DAP were not different between groups, although MAP was significantly higher in the ketofol group compared to the propofol group (82 ± 10 mmHg) compared to the propofol group (77 ± 11 mmHg) (p = 0.05). When comparisons were made with baseline blood pressure, the decreases observed were similar in both groups (Table 3).

There was no difference in f_R before induction of anaesthesia between groups [propofol 40 (15–195) breaths minute⁻¹ and ketofol 41 (10–167) breaths minute⁻¹] (Table 4). Ketofol resulted in a greater decrease in f_R (−32 [−158 to 0] breaths minute⁻¹) than propofol (−24 [−187 to 2] breaths minute⁻¹) (p < 0.0001). Time to the first breath was not statistically different between propofol (8 [2–60] seconds) and ketofol (20 [2–60] seconds) (p = 0.07). Manual ventilation was needed in two dogs in the propofol group and four in the ketofol group because SpO₂ decreased below 92%.

Quality of sedation after premedication (Table 5) was similar between groups [propofol 2 (0–2) and ketofol 2 (1–3) p = 0.38]. Quality of tracheal intubation and anaesthetic induction were significantly better when anaesthesia was induced with ketofol [0 (0–1) and 0 (0–0) respectively] than with propofol [1 (0–3) and 0 (0–2)] (p = 0.04 and 0.02 respectively).
No adverse events attributable to the induction agent/s were detected in any of the patients in the study.

Discussion

In this study the propofol-ketamine admixture known as ketofol allowed tracheal intubation with a smaller propofol dose than when propofol was administered alone. Ketofol use was associated with higher PR and MAP, and superior quality of tracheal intubation and induction of anaesthesia, compared with the use of propofol alone, however respiratory rate was lower when ketofol was administered.

Drug doses required for tracheal intubation were 4 ± 1 mg kg⁻¹ of propofol alone, or 1.8 ± 0.9 mg kg⁻¹ of each propofol and ketamine. Weaver & Raptopoulos (1990) reported an induction dose of propofol in dogs of 3.6 ± 1.4 mg kg⁻¹ following pre-anaesthetic medication. Similar values have also been reported in dogs medicated with acepromazine and morphine (3.51 ± 0.74 mg kg⁻¹) (Covey-Crump & Murison 2008). The dose of propofol reported here is slightly higher than these reported doses. This slight variation might be due to the use of a different rate of administration or target point, and its clinical importance is questionable. The dose of ketofol required was substantially greater than the doses reported in people. Andolfatto & Willman (2010) used 0.8 mg kg⁻¹ each of ketamine and propofol in procedural sedation and propofol in the trauma emergency department and Erdogan et al. (2013) achieved laryngeal mask placement after the administration of 0.75 mg kg⁻¹ ketamine plus 0.75 mg kg⁻¹ propofol. This difference is likely to be due to tracheal intubation requiring a greater dose of induction agent than the application of a supraglottic device (Wiederstein et al. 2006). In regards to the sparing on propofol dose when ketofol is used, Phillips et al. (2010) reported that human patients receiving propofol alone required twice the amount to achieve adequate sedation than those patients who received propofol/ketamine. This result is comparable with the reduction in dose reported here.

The administration of propofol is generally associated with a decrease in PR and arterial blood pressure (ABP). This depression is believed to be a dose-dependent lowering of sympathetic tone, in addition to direct negative inotropic and venodilator effects (Goodchild & Serrao 1989). A mild increase in PR was observed in this study. Induction of anaesthesia with propofol in dogs has previously been associated with both a decrease in PR (Lerche & Nolan 2000) or a mild increase (Jolliffe et al. 2007; Intelisano et al. 2008; Sams et al. 2008). Ketofol was associated with a greater increase in PR in this study. In humans, Phillips et al. (2010) reported a trend for ABP and PR to be more stable with ketofol compared to propofol, although no statistical significance was found. Although the difference in cardiovascular response after induction of anaesthesia may be attributable to interspecies variation, it is plausible that it reflects the differences between anaesthetic protocols in human and veterinary medicine. Endotracheal intubation is very common in veterinary medicine and it is known to produce a greater sympathetic stimulation than laryngeal mask placement in humans, characterized by an increase in PR, ABP, intraocular pressure, and stress hormones (Agrawal et al. 2012; Carron et al. 2012). Ketamine induces sympathetic activation, which may contribute to the results obtained in this study, but it does not fully explain the difference between the human and the animal results from the literature. Propofol attenuates the sympathetic responses and reflex responses to hypotension (Rocchiccioli et al. 1989; Ebert & Muzi 1994), it might be speculated that the combination of propofol with ketamine may antagonise this attenuation due to a counteraction of pharmacological effects or a dose reduction of the most disadvantageous drug. In our study Ketofol resulted in higher MAP than propofol. Similar effects have been observed in dogs after ketamine (2 mg kg⁻¹) and propofol (2 mg kg⁻¹) for induction of anaesthesia (Lerche & Nolan 2000) and in people, when propofol was compared with propofol/ketamine administered in the same syringe (Smischney et al. 2012) or in separate syringes (Hui et al. 1995).

Propofol is known to produce respiratory depression when used for induction of anaesthesia (Smith et al. 1994). Ketamine, at normal clinical doses, has minimal effect on respiratory drive, although a transient decrease in ventilation can occur after rapid bolus administration when administered with midazolam in dogs (Jacobson & Hartsfield 1993). In this study, ketofol produced a greater decrease in respiratory rate than propofol. This contrasts with previous reports of ketofol in the literature. Hui et al. (1995) reported that the addition of ketamine to propofol did not worsen the apnoea compared to propofol alone, and in children and the elderly, ketofol resulted in less respiratory depression compared to propofol (Frey et al. 1999; Akin et al. 2014).
Ketofol has also been seen to cause minimal or no ventilatory depression when post-induction values were compared to baseline measurements in both humans and cats (Morse et al. 2003; Green et al. 2011; Ravasio et al. 2012). In contrast, Lerche & Nolan (2000) described apnoea in 73% (11 out of 15) of dogs when 2 mg kg\(^{-1}\) ketamine was administered following 2 mg kg\(^{-1}\) propofol for induction of anaesthesia, whereas propofol (4 mg kg\(^{-1}\)) produced apnoea in 40% (6 of 15). These results seem to agree with our findings. This greater decrease in respiratory rate compared to other species may be due to a different and/or inadequate rate of administration, although a particular sensitivity of dogs to ketamine cannot be totally ruled out.

Respiratory effects were only assessed by measuring \(f_R\). Additional information such as end-tidal CO\(_2\) and minute volume would have been useful in evaluating respiratory function.

Induction of anaesthesia with propofol is associated with excitatory phenomena such as limb paddling, muscle twitching and opisthotonus in 7.5–9% of dogs (Davies 1991; Covey-Crump & Murison 2008). Mild to moderate muscle twitching and limb movement were seen in 31.6% (11 out of 34) dogs induced with propofol alone in our study. These results are similar to the 23.3% reported by Michou et al. (2012).

The combination of two or more drugs to achieve induction of anaesthesia is known as ‘coinduction’ (Amrein et al. 1995). Coinduction aims to decrease doses and adverse effects of the drugs used. The only difference between coinduction and ketofol induction is that for the latter the drugs are mixed in the same syringe before administration. For this reason, it might be presumed that the addition of ketamine to propofol should attenuate the excitation occasionally seen during induction in the same way that other drugs such as fentanyl (Covey-Crump & Murison 2008) and midazolam (Sánchez et al. 2013) do, however, this beneficial effect was not seen by Lerche & Nolan (2000) or Seliskar et al. (2007) when propofol and ketamine were administered in separate syringes. The difference observed between the reports using propofol and ketamine in separate syringes or mixed together might be due to the varying onset times of the drugs when mixed together. It has been recently speculated that dosing individually each drugs may be superior to the combination of them (Shy & Howland 2013).

Whether two syringes are superior, worse or different to ketofol is not known, as there is no evidence in any species comparing both methods of dosing.

The institutional ethics committee recommended exclusion of patients with anaesthetic period shorter than one hour, due to previously reported poor emergence from anaesthesia when ketamine is administered alone (White et al. 1982). This study was not designed to assess anaesthetic recovery quality, however clinically, no poor recoveries were noted. Ketofol has been observed to produce smooth recoveries in other species (Ravasio et al. 2012; Smischney et al. 2012).

This study has some limitations, the majority of them related to its clinical nature. Firstly, the injection of the study drugs was performed by hand injection that may have introduced some variation in the rate. The use of a syringe driver would have allowed a constant administration rate without any potential human variability. Secondly, the parameters were measured after tracheal intubation and not immediately after induction of anaesthesia. Endotracheal intubation was considered essential in our research for patients’ safety after the use of drugs with known respiratory depression effect. As discussed above, this manoeuvre might have masked some subtle haemodynamic changes between propofol and ketofol, due to the strong sympathetic stimulation that it triggers. Finally, respiratory values other than \(f_R\) were not obtained before induction of anaesthesia. This limited very much the assessment of the degree of respiratory depression that propofol and ketofol produced.

In conclusion, ketamine/propofol mixture (ketofol) maintained superior haemodynamic parameters than propofol, but resulted in greater respiratory depression. It also provided better tracheal intubation and induction of anaesthesia characteristics.

Acknowledgements

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Supporting Information
Additional Supporting Information may be found in the online version of this article:
Appendix S1. Quality scoring systems.