The effect of opioid and acepromazine premedication on the anesthetic induction dose of propofol in cats

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Abstract — The median effective dosage (ED_{50}) for induction of anesthesia with propofol was determined by using the up-and-down method in 31 unpremedicated cats, in 30 cats premedicated with butorphanol, 0.4 mg/kg body weight (BW), and acepromazine, 0.1 mg/kg BW, intramuscularly, and in 30 cats premedicated with morphine, 0.2 mg/kg BW, and acepromazine, 0.1 mg/kg BW, intramuscularly. The dose required for a satisfactory anesthetic induction in 50% of unpremedicated cats (ED_{50}) was 7.22 mg/kg BW and of premedicated cats was 5.00 mg/kg BW. The reduction in dose was statistically significant in both premedicated groups compared with no premedication. There was no significant difference in ED_{50} between premedication regimes. Cyanosis was the most common adverse effect observed in all groups following anesthetic induction with propofol.

Résumé — Effets d'une prémédication aux opioïdes et à l'acépromazine sur la dose de propofol nécessaire à l'induction de l'anesthésie chez le chat. La dose efficace médiane (DE_{50}) pour l'induction de l'anesthésie au propofol a été déterminée par la méthode des doses croissantes et décroissantes chez 31 chats non-traités, chez 30 chats prétraités au butorphanol, 0.4 mg/kg de poids corporel (PC) et acépromazine 0.1 mg/kg PC, par voie intramusculaire et chez 30 chats prétraités à la morphine, 0.2 mg/kg PC et acépromazine 0.1 mg/kg, PC intramusculaire. La dose nécessaire pour induction satisfaisante de l'anesthésie chez 50 % des chats non-traités (DE_{50}) était de 7.22 mg/kg PC, et des chats prétraités était de 5.0 mg/kg PC. La réduction du dosage étais statistiquement significative chez les 2 groupes prétraités en comparaison avec le groupe non-traité. Il n'y avait pas de différence significative dans la DE_{50} entre les 2 types de prémédication. La cyanose était la réaction indésirable le plus fréquemment observée chez tous les groupes suite à l'induction de l'anesthésie au propofol.

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Introduction

Propofol, an alkylphenol derivative, is a short acting, nonaccumulating, injectable, general anesthetic agent that is licensed for use in the cat and dog. The company drug data sheet indicates that the anesthetic induction dose in the unpremedicated cat is 8 mg/kg body weight (BW); if the cat is premedicated with a tranquillizer, such as acepromazine, the dose is 6 mg/kg BW, based on studies published elsewhere (1). Premedication of veterinary patients with a tranquillizer and an opioid prior to induction of anesthesia is desirable, because it provides restraint, sedation, analgesia, and reduces the requirements of induction and maintenance anesthetic agents. Previous trials have investigated the effects of premedication on the anesthetic induction dose of propofol by using a variety of agents. Acepromazine was commonly used alone or in combination with atropine (2–4) or meperidine (3). One study did not accurately specify the premedicant drugs and doses used (5). The aim of this trial was to further investigate the dose of propofol required to induce satisfactory anesthesia in the cat and to determine the effect of 2 commonly used premedication protocols. The technique used to determine the suitable induction dose of propofol was based on previously published work in dogs (6).

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Reprints will not be available.

Propofol for this project was provided by Mallinckrodt Veterinary, Inc., Ajax, Ontario.

Materials and methods

Patient selection and preparation

Ninety-one domestic cats presented to the Veterinary Teaching Hospital at the Western College of Veterinary Medicine were used in this study. The cats were scheduled to undergo routine elective surgical or medical procedures. All cats were weighed and assessed as American Society of Anesthesiologists status I or II, based on normal physical and hematological examinations. The minimum hematological database consisted of packed cell volume, total protein, and blood urea nitrogen. No age restrictions were placed. Most of the cats, however, were recruited from those admitted for spay ($n = 46$), castration ($n = 36$), and/or onchyectomy ($n = 4$) and were less than 1 y of age. Other procedures included laryngeal mass biopsy ($n = 1$), lateral ear resection ($n = 1$), conjunctival biopsies ($n = 1$), transtracheal wash ($n = 1$), and vaccine reaction lump removal ($n = 1$). Cat breeds included domestic short or long hairs (89/91), American shorthair (1/91), and Norwegian forest cat (1/91).

Food and water were withheld from the cats at least 12 h and 2 h, respectively, prior to induction of anesthesia. Cats were allocated to 1 of the 3 groups by the senior veterinary student assigned to the patient. Cats chosen for the premedicated groups were given acepromazine (Atravet; Ayerst Laboratories, Montreal, Quebec), 0.1 mg/kg body weight (BW), combined with either butorphanol (Torbugesic, Ayerst Laboratories), 0.4 mg/kg BW (Group BA, 30 cats), or morphine (Morphine sulphate, Sabex, Boucherville, Quebec), 0.2 mg/kg BW, (Group MA, 30 cats). Premedicant drugs were given by intramuscular (IM) injection 20 to 30 min prior to induction of anesthesia. The remaining cats were not premedicated (Group U, 31 cats).

Propofol administration

Prior to anesthetic induction with propofol (Rapinovet, Mallinckrodt Veterinary, Ajax, Ontario), a 22-gauge, over-the-needle catheter (Surflo IV catheter, Terumo Medical Corporation, Elkton, Maryland, USA) or a 21-gauge, butterfly needle (Venisystems, Abbott, Sligo, Ireland) was aseptically placed in either the cephalic vein or the medial saphenous vein.

The test dose of propofol to be administered was determined by using the up-and-down method, based on previously reported studies in dogs (6,7). The first unpremedicated cat was given 6 mg/kg BW of propofol, IV. The first cat in group MA and in group BA was given 4 mg/kg BW of propofol, IV. If the anesthetic induction was judged to be satisfactory by using the criteria listed below, the test dose was reduced by 20% for the following cat. Conversely, if the induction of anesthesia was judged to be unsatisfactory, the following cat received a 25% increase in the test dose. This method was repeated for subsequent cats in each group, with the anesthetic induction test dose being increased or reduced, depending on the quality of anesthetic induction observed in the preceding cat. The quality of the anesthetic induction was judged by the same experienced anesthetist (TLH).

The test dose of propofol was administered over 10-15 s, and the catheter immediately flushed with lactated Ringer's solution (Lactated Ringer's Injection USP, Abbott Laboratories, Montreal, Quebec) or heparinized saline [(500 IU heparin (Hepalean, Organon Tekniko, Toronto, Ontario) added to 500 mL saline (Physiologic saline, MTC Pharmaceuticals, Cambridge, Ontario)] to ensure that the cat received the full test dose. Thirty seconds after commencing the propofol injection, the larynx was sprayed with lidocaine topical spray (Xylocaine, Astra Pharma, Mississauga, Ontario). Tracheal intubation was attempted 60 s after commencing injection of propofol. Anesthesia was maintained by either halothane (Halothane, Halocarbon Laboratories, River Edge, New Jersey, USA) or isoflurane (Isoflurane USP, Abbott Laboratories) in oxygen.

The criteria used to define satisfactory anesthetic induction were the conditions required for tracheal intubation; that is, lack of jaw tone and absence of coughing or swallowing or minor attempts that did not hinder tracheal intubation. Unsatisfactory conditions included muscle rigidity, struggling, chewing movements, marked swallowing, or poor transition to inhalational anesthesia. If the induction was judged unsatisfactory further increments of 25% of the test dose were administered until induction of anesthesia was complete. These increments were not included in the calculation of the induction dose for subsequent cats, but this dose was recorded (total dose). Any adverse reactions observed during induction of anesthesia were recorded. All procedures were performed by senior veterinary students or veterinary technologists under direct supervision of an experienced anesthesia technician or by a clinician (TLH).

Statistical analysis

The outcomes of interest in this study were the doses of propofol required to achieve satisfactory anesthetic induction in 50% (ED_{50}) and 100% (ED_{100}) of the cats. The independent variable of interest was the premedication or treatment regime (no premedication, acepromazine plus butorphanol, and acepromazine plus morphine). The doses of propofol were slightly skewed in some cases and, therefore, the results are expressed in terms of the median. For each treatment group, the median ED_{50} was calculated from the doses yielded by the up-and-down method and the median ED_{100} from the total dose of propofol given to each cat.

The effect of treatment on the dose of propofol was assessed by using the Kruskal-Wallis one-way analysis of variance procedure. Subsequent comparisons of the medians were tested by comparing the mean of the ranks. The ranks of the propofol doses were regressed upon the variables sex, age, BW, and treatment, in order to examine the combined effect of these variables. All calculations were performed by using a commercial statistical software package (Statistix for Windows, Analytical Software, Tallahassee, Florida, USA). Only those results where $P < 0.05$ were considered statistically significant.

Results

Demographics of the cats included in the study are summarized in Table 1. After controlling for the effects

Table 1. Demographics of cats in the study

Variable	Group		
	Unpremedicated	Butorphanol + acepromazine	Morphine + acepromazine
Age (mo)	8.0; 4.0–48.0	12.0; 5.0–120.0	9.0; 5.0–60.0
Body weight (kg)	3.3; 1.5–5.0	3.0; 2.1–4.9	2.9; 2.3–5.7
Sex (M/F)	21/10	10/20	6/24

Data for age and body weight are expressed as median; range.

Table 2. Adverse reactions recorded during administration of propofol

	Group		
	Unpremedicated	Butorphanol + acepromazine	Morphine + acepromazine
Cyanosis	14	7	4
Twitching ears/ facial muscles	2	2	0
Opisthotonos	0	1	0
Sneezing	1	0	0
Pain on injection	1	0	0

of premedication, the age, sex, and BW of the cats did not influence either the ED_{50} or the total dose of propofol (ED_{100}).

In the unpremedicated group, the range of dose for satisfactory induction was 6.0 to 11.7 mg/kg BW (n = 14), while the range of dose for unsatisfactory anesthetic induction was 5.0 to 9.4 mg/kg BW (n = 17). In group BA, the range of dose for satisfactory anesthetic induction was 4.0 to 7.8 mg/kg BW (n = 15), while range of dose for unsatisfactory anesthetic induction was 3.2 to 6.8 mg/kg BW (n = 15). In group MA, the range of dose for satisfactory anesthetic induction was 4.0 to 6.25 mg/kg BW (n = 14), while range of dose for unsatisfactory anesthetic inductions was 3.2 to 5.0 mg/kg BW (n = 16).

In the unpremedicated group, the dose of propofol producing satisfactory anesthetic induction in 50% of cats was 7.27 mg/kg BW, while the dose required to produce satisfactory anesthetic induction in all cats was 8.33 mg/kg BW. These doses were significantly higher than the doses required when premedication was used ($P < 0.001$). The ED_{50} and ED_{100} did not differ significantly between the 2 groups where premedication was used. The dose required to produce satisfactory anesthetic induction in 50% of the cats that were premedicated was 5.00 mg/kg BW and the dose required to produce satisfactory anesthetic induction in all premedicated cats was 5.64 mg/kg BW in group BA and 5.97 mg/kg BW in group MA.

Adverse reactions at anesthetic induction included cyanosis, twitching ears and facial muscles, opisthotonos, sneezing, and pain on injection (Table 2). In the unpremedicated group, the majority of cyanotic cats were those receiving higher doses of propofol (mean, 7.8 mg/kg BW) when compared with premedicated cats (mean, 4.08 mg/kg BW in MA and 5.4 mg/kg BW in BA).

Discussion

Premedication techniques are used to provide sedation and restraint in order to facilitate handling of patients, to contribute to analgesia, and to lower doses of major anesthetic agents. In this study, the results indicate that premedication of cats with an opioid and acepromazine compared with no premedication allows approximately a 30% reduction in the dose of propofol required to produce conditions for satisfactory anesthetic induction. This is similar to the 25% reduction in dose attributed to premedication with various agents reported by Morgan and Legge (5).

It is difficult to directly compare our study with those of others as we used the up-and-down method and others used incremental dose bolusing with tracheal intubation as an endpoint. Incremental bolus injection tends to create higher mean values than those obtained by using the up-and-down method (6). The up-and-down dosing method was used to determine the ED_{50} of propofol, as it requires using fewer animals for significant results (7). However, this method creates the problem of having very few animals in the outlying doses, as it tends to quickly bring the doses toward the median. It cannot be assumed that all cats will have satisfactory anesthetic induction at the highest dose and that all will have unsatisfactory anesthetic induction at the lowest dose recorded in our study. A further sampling of cats given fixed doses at these high and low dose ranges would give a more accurate depiction of the dose-response curve.

In this study, the ED_{50} for propofol in premedicated groups is similar to endpoint anesthetic induction doses in premedicated cats described by Weaver and Raptopoulos (5.3 ± 4.3 mg/kg BW) (3) and Morgan and Legge (5.97 mg/kg BW) (5), but is not similar to that found by Brearley et al (6.8 mg/kg BW) (2), or Geel (7.1 mg/kg BW) (4). Drugs and doses used for premedication varied between and within studies or were not specified, which makes comparison of studies difficult.

In humans, inclusion of an opioid in the premedication should reduce the dose of propofol required for anesthetic induction (8). Similarly, it is expected that premedication with an opioid will reduce requirements of anesthetic induction agents in other species. It is difficult to know whether it was the opioid, the tranquillizer, or the combination of these agents that allowed the reduction in propofol induction dose found in this study. We cannot eliminate acepromazine as causing the reduction in dose in this study, because of the conflicting results that have been obtained in other studies. Some authors determined that premedication of cats with acepromazine caused a reduction in the anesthetic induction dose of propofol (5), while others found that this premedication did not cause a reduction in dose (2–4).

The criteria used in this study to judge quality of anesthetic induction are similar to those used by Watney and Pablo (6) in determining the ED_{50} of propofol in dogs. The decision to judge an induction as satisfactory or unsatisfactory based on these criteria was not ideal. Many cats reacted to the spraying of the larynx at 30 s (marked jaw tone, chewing, coughing when sprayed). These cats, however, generally had very smooth transition to anesthesia. Many cats in which endotracheal intubation was difficult but achieved (chewing, marked jaw tone) and induction, therefore, questionable also had very smooth transition to inhalant anesthesia. The

addition of a ranking system incorporating the components of anesthetic induction in addition to using the above criteria might have been helpful in making decisions on how to judge the questionable anesthetic inductions. It seemed that attempts to intubate the trachea at 60 s after the start of injection were premature in many cats, and waiting longer might have achieved more satisfactory results. Watney and Pablo (6) did not report problems with endotracheal intubation of dogs at 60 s after the start of injection. The longer time required to achieve conditions that allow endotracheal intubation in cats may be due to the additional stimulation of opening the mouth and spraying the larynx at 30 s after the start of injection.

The premedication regimes used in this study are routine premedicants used in the anesthesia department of this college. Students assigning cats to groups initially chose a premedication regime based on personal preference or previous experience but were encouraged to try a different premedication or no premedication for experience. They were required to place subsequent cats under their care into a premedication group different from their initial choice. Although this did not make the assignation random in the strict sense, it did eliminate any patient selection bias by the supervising anesthetist and removed some student selection bias. At the time of catheter placement, the supervising clinician was usually unaware to which group the cat had been assigned. It seemed that the cats premedicated with butorphanol and acepromazine were more tolerant of catheter placement and clipping of hair than those premedicated with morphine and acepromazine. This difference, however, was not recorded or quantified and cannot be proven in this study. At anesthetic induction, the supervising anesthetist was not blinded to which treatment group the cats had been allocated. Blinding of the anesthesia clinician would have been preferable but was impractical. Although some cats had questionable anesthetic inductions, the criteria for judging them as satisfactory or not were adhered to and, therefore, any introduction of bias was probably minor. The cats that had questionable anesthetic inductions were not more prevalent in any one group.

The majority of cyanotic cats were in the unpremedicated group. Cyanosis from propofol seems to occur from respiratory depression (9,10), but myocardial depression (11,12), hypotension from venodilation (13,14), and arteriodilation (12,15,16) may also contribute. As test doses of propofol were not standard across groups, the number of cyanotic animals receiving each dose cannot be compared. Cyanosis at lower anesthetic induction doses in the premedicated groups probably reflects the accentuated induction apnea seen with opioid premedication and propofol (10). Other authors have reported induction apnea as their most common adverse effect, and was attenuated by slower administration of propofol (2,5). There may have been fewer occurrences of cyanosis in our study cats, if the test bolus had been injected over a longer period of time. In the anesthesia department of this college, half the calculated total dose of propofol is delivered as a rapid bolus followed by titration of the remaining half as needed until satisfactory conditions for endotracheal intubation are achieved. Our total calculated doses are similar to the manufacturer's recommended anesthetic induction doses.

The results of this trial indicate that cats premedicated with butorphanol or morphine combined with acepromazine required significantly reduced the amounts of propofol for induction of anesthesia compared with cats receiving no premedication. Cyanosis was the most common side effect noted in all groups, and it was observed at lower anesthetic induction doses in premedicated cats vs unpremedicated cats.

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