

Evaluation of diphenhydramine as a sedative for dogs

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Objective—To determine and compare levels of sedation achieved by IM administration of diphenhydramine, saline (0.9% NaCl) solution, and acepromazine in dogs.

Design—Prospective randomized study.

Animals—56 dogs.

Procedure—Dogs were randomly assigned to receive diphenhydramine at 2, 4, or 8 mg/kg (0.9, 1.8, or 3.6 mg/lb, respectively) IM; acepromazine at 0.1 mg/kg (0.05 mg/lb) IM; or saline solution at 0.05 mL/kg (0.02 mL/lb) IM. Sedation was assessed by use of a 6-category descriptive system based on observation and interaction.

Results—Dogs in the acepromazine group had significantly higher sedation scores than did dogs in the saline solution or diphenhydramine groups at 30 minutes. Dogs in the diphenhydramine groups did not have significantly different sedation scores from dogs in the saline solution group at any time point.

Conclusions and Clinical Relevance—Diphenhydramine did not cause clinically appreciable sedation in healthy dogs. Diphenhydramine is not suitable as a sole sedative prior to general anesthesia in dogs. (*J Am Vet Med Assoc* 2005;226:1092–1094)

Diphenhydramine is an H1 receptor antagonist used in a variety of allergic conditions.¹ Because of its antihistaminic and anticholinergic properties, it may cause sedation as an adverse effect in humans.² Because of this effect, many practitioners use diphenhydramine for mild sedation in dogs, including sedation for travel, during stressful experiences, or before anesthetic induction. Diphenhydramine is frequently used in our hospital as a premedication agent before anesthesia in patients with mast cell tumors in an attempt to decrease histamine effects that result from degranulation of mast cells associated with tumor manipulation. Diphenhydramine is inexpensive, is not a controlled substance, causes minimal cardiovascular suppression, and is readily accessible to general practitioners. All these qualities make it a potentially valuable drug for use as a sedative before anesthesia.

In humans, diphenhydramine causes drowsiness, impedes performance on mental cognition tests, and

slows physical reaction time.^{3,4} It is indicated for use in allergic conditions, motion sickness, and Parkinson's disease.⁵ In a survey⁶ of 19,108 patients after conscious surgery for cataract removal, inclusion of diphenhydramine in the preanesthetic protocol resulted in substantial reduction in incidence of pain during surgery; reduction in dissatisfaction with pain management; and reduction in incidence of postoperative drowsiness, nausea, and vomiting. If diphenhydramine had similar effects in dogs, its routine inclusion as part of a preanesthetic medication would be warranted.

The sedative effects of diphenhydramine in dogs have been reported only in a secondary reference⁷ and have not been specifically studied in a prospective, randomized, controlled research trial. The purpose of the study reported here was to determine the sedative effects of administration of diphenhydramine in dogs.

Materials and Methods

Fifty-six random-source (obtained from municipal shelters), mixed-breed dogs that were anesthetized for a surgical exercises laboratory were used in the study. There were 8 dogs in a negative control group that received only saline (0.9% NaCl) solution and 12 dogs in each of 4 other groups. The protocol was approved by the University of Georgia Animal Care and Use Committee, and husbandry was provided according to established institutional guidelines. Any dog deemed unhealthy because of results of physical examination or with an abnormal PCV or total protein concentration was excluded. **Body condition score (BCS)** was assessed by use of a previously published system.⁸ Dogs were randomly assigned to groups that received saline solution (0.05 mL/kg [0.02 mL/lb], IM), diphenhydramine^a (2, 4, or 8 mg/kg [0.9, 1.8, or 3.6 mg/lb, respectively] IM), or acepromazine^b (0.1 mg/kg [0.05 mg/lb], IM [positive control group]). All IM injections were made in the caudal epaxial musculature by an experienced individual.

A single individual (EHH), blinded to treatment group, performed all sedation scoring. Dogs were housed individually during sedation scoring and for at least 12 hours before initiation of the study. Dogs were acclimated to the presence of the observer for approximately 10 minutes before administration of a test substance. During data collection, the dogs were allowed to move freely in their cages. Sedation scores were obtained before administration and at 10, 20, and 30 minutes after administration by use of a modification of a previously published objective scoring system.⁹ A score for analgesia was removed from the original system because none of the drugs administered in this study would be expected to provide analgesia. The total sedation score for each dog at each time point was calculated by adding all values for all 6 categories together. Any adverse effects were recorded. Between recordings, the observer walked between dog cages, further acclimating the dogs to the observer's presence.

The sedation data were analyzed for normality, and parametric statistics were used for data analysis. For sedation scores, weight in kilograms, and BCS, a 1-way ANOVA was used for comparisons among groups. Post hoc analysis was performed by

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The authors thank Dr. C. Rawlings for technical assistance. Address correspondence to Dr. Hofmeister.

Table 1—Mean \pm SD sedation scores in dogs given diphenhydramine (2, 4, or 8 mg/kg [0.9, 1.8, or 3.6 mg/lb, respectively], IM, [D2, D4, and D8, respectively]), acepromazine (0.1 mg/kg [0.05 mg/lb], IM [ACE]), or saline (0.9% NaCl) solution (0.05 mL/kg [0.02 mL/lb], IM [SAL]) before (time 0) and 10, 20, and 30 minutes after administration.

Group	Time (min)			
	0	10	20	30
D2	-3.25 \pm 3.33	-0.67 \pm 2.77 ^a	0.0 \pm 2.89 ^a	1.0 \pm 2.89 ^a
D4	-0.58 \pm 3.37	0.25 \pm 2.8	1.0 \pm 2.95	1.75 \pm 3.86 ^a
D8	-1.08 \pm 2.54	1.83 \pm 2.25 ^a	2.0 \pm 2.80 ^a	3.08 \pm 2.15 ^a
ACE	-2.33 \pm 4.14	1.17 \pm 2.95 ^a	3.17 \pm 3.16 ^a	6.08 \pm 2.97 ^{a,b}
SAL	-2.13 \pm 4.91	-0.63 \pm 3.58	1.13 \pm 4.32 ^a	1.5 \pm 3.89 ^a

Maximum possible sedation score is 14.
^aSignificantly ($P < 0.05$) different from value at time 0.
^bSignificantly ($P < 0.05$) different from SAL, D2, D4, and D8 at this time point.

use of the Tukey multiple-comparison test. A 1-way ANOVA for repeated measures was used to test for changes within a treatment group over time. When significance was found, post hoc analysis was performed by use of the Tukey multiple-comparison test. A commercial statistical software package was used for all analyses.^c Statistical significance was set at $P < 0.05$.

Results

There were no significant differences among groups for weight or BCS. There were no significant differences among groups for sedation scores at 0, 10, and 20 minutes. At 30 minutes, mean sedation score in the acepromazine group was significantly higher than that in the saline solution or diphenhydramine groups. Sedation scores increased over time for all groups (Table 1). No adverse reactions were observed during sedation scoring, catheter placement and induction, or anesthetic maintenance periods in any of the groups.

Discussion

The data from this study suggest that diphenhydramine given IM at 2, 4, and 8 mg/kg does not induce substantial sedation within 30 minutes of injection. These results are in conflict with anecdotal reports.

There was a significant increase in sedation scores over time for all groups, including the negative control group that received only saline solution. In other studies^{10,11} that used a similarly detailed sedation scoring system, sedation over time was also observed in control groups. This suggests that there may have been acclimation to the investigator's presence during evaluation. Because all 5 groups had increased sedation scores over time, we do not believe that this observation invalidates our findings. Ideally, dogs should have been acclimated to the process of sedation scoring over several days and over a greater time before sedation than was done. However, these dogs were available only for a limited amount of time before initiation of a student laboratory exercise.

It is possible that the system we used was not sufficiently sensitive to detect a difference in sedation between the saline solution control group and the diphenhydramine groups. We selected the sedation scoring system of Smith et al⁹ because of its ease of use, perceived reduction in subjectivity, sensitivity to minor sedation changes, and familiarity. Sedation scoring systems in the literature range from nonblinded, simple 1-

to-5 scoring systems to systems as detailed as the one used in the study reported here.¹⁰⁻¹² None of the sedation scoring systems reviewed in the veterinary literature has been fully validated. A more detailed scoring system could not be located in the literature or independently derived, so we believe that the system we used was as sensitive as possible in a clinical setting.

It is possible that diphenhydramine causes sedation only after oral administration. The pharmacokinetics of diphenhydramine in dogs have been evaluated only in 1 publication, which reported data from only 2 dogs.¹³ Thus, we cannot comment on the bioavailability or plasma concentrations of diphenhydramine after administration PO or IM, and we cannot correlate sedation levels with plasma concentrations of the drug because this was not investigated.

We recorded sedation scores for 30 minutes after administration, which may have been inadequate for efficacious plasma concentrations to be reached. However, in cats, behavior changes were observed as early as 30 minutes after oral administration of diphenhydramine at 3 mg/kg (1.4 mg/lb).¹⁴ We chose to stop recording sedation at 30 minutes because, when evaluated for use as a sedative before anesthesia, an onset time > 30 minutes is not likely to be clinically useful. However, if sedation occurs at a later time point, the drug may contribute to increased anesthetic depth or prolonged recovery time after general anesthesia.

The dogs in the present study were all random-source, healthy young dogs. Many were either quite agitated and energetic or somewhat frightened and timid. This did not necessarily represent the population in most small animal clinics that might use diphenhydramine. Because of their initial state of excitement and excitability, it is possible that these dogs were able to overcome any mild sedative effects caused by the diphenhydramine.¹⁵

Other studies have detected conflicting results with diphenhydramine administration in dogs. In 1 study¹⁶ in which diphenhydramine (30 to 45 mg/kg [13.6 to 20.5 mg/lb]) was administered orally, dogs became stimulated, had tremors, and had increased reactivity and muscle tone. In another study¹⁷ in dogs, orally administered diphenhydramine at 10 mg/kg (4.5 mg/lb) increased slow wave sleep and increased time spent in the transition to sleep (drowsiness).

We believe the most likely explanation for the discrepancy between our results and anecdotal reports was not related to methodology but rather to a difference in study population, a difference in route of administration, or the placebo effect. Regardless, when evaluated as a medication for use as a sedative prior to anesthesia, diphenhydramine was not clinically useful.

A dose of 2 mg of diphenhydramine/kg is used clinically in our hospital for antihistamine prophylaxis against mast cell tumor degranulation. Selection of 4 and 8 mg/kg represents 2 and 4 times this dose, respectively. It was hoped that these doses would be successful in elucidating a dose-response curve for sedation. In addition, it was believed that these doses would be safe to administer to dogs and would not result in severe adverse reactions that would be unacceptable in the teaching laboratory setting. We found that doses up to 8 mg/kg did not induce any obvious adverse effects.

Acepromazine was used as a positive control because of our extensive experience with this drug, its predictable and reliable sedation, and its wide safety margin. The sample size for the negative control group (saline solution) was smaller than the other groups because we believed the response of negative control dogs (ie, lack of sedation) would be more predictable than dogs given a treatment. In addition, we were more interested in comparing diphenhydramine and acepromazine than diphenhydramine and saline solution because it was believed that diphenhydramine would induce at least some level of sedation.

A randomized crossover design in which each dog served as its own control would have been ideal and may have helped to reduce some of the confounders in this study. Individual dog variations such as behavior and excitement would have been minimized. However, given the laboratory and housing constraints used in our protocol, this was impossible.

Evaluating sedation scores over a longer period of time after injection, investigating the effects of orally administered diphenhydramine, determining the effect of diphenhydramine in cats, determining the sedative effects when combining diphenhydramine with another sedative, and investigating the pharmacokinetics of orally and parenterally administered diphenhydramine in dogs and cats may be useful. Nevertheless, on the basis of the results of this study, we do not recommend IM administration of diphenhydramine at the doses investigated for the purpose of providing sedation prior to anesthesia in dogs.

- a. Elkins-Sinn Inc, Cherry Hill, NC.
- b. Boehringer Ingelheim Vetmedica Inc, St Joseph, Mo.
- c. Graphpad Prism, Graphpad Software Inc, San Diego, Calif.

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Correction: Red blood cell transfusions in cats: 126 cases (1999)

In the article “Red blood cell transfusions in cats: 126 cases (1999),” published in the March 15, 2005, issue (2005;226:920–923), references 14 through 16 were omitted from the reference list during production. The omitted references appear below and the correct version of the article can be found in its entirety online at www.avma.org.

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