Effects of hydromorphone or oxymorphone, with or without acepromazine, on preanesthetic sedation, physiologic values, and histamine release in dogs

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Objective—To compare hydromorphone with oxymorphone, with or without acepromazine, for preanesthetic sedation in dogs and assess changes in plasma concentration of histamine after drug administration.

Design—Randomized clinical study.

Animals—10 healthy mixed-breed dogs.

Procedure—Dogs were treated IM with hydromorphone (group H), oxymorphone (group O), hydromorphone with acepromazine (group H/A), or oxymorphone with acepromazine (group O/A). Sedation score, heart rate, respiratory rate, systolic blood pressure, and oxygen saturation were recorded at baseline immediately after drug administration (T0) and every 5 minutes for 25 minutes (T25). Plasma histamine concentration was measured at baseline and T25.

Results—Sedation was similar between groups H and O at all times. Sedation was significantly greater for groups H/A and O/A from T10 to T25, compared with other groups. Systolic blood pressure was significantly reduced at T25 in group H/A, compared with group H, and in group O/A, compared with group O. Prevalence of panting at T25 was 50% for groups H and O, compared with 20% for group H/A and 30% for group O/A. By T25, heart rate was significantly lower in all groups. Oxygen saturation was unaffected by treatment. Mean ± SD plasma histamine concentration was 1.72 ± 2.69 ng/ml at baseline and 1.13 ± 1.18 ng/ml at T25. There was no significant change in plasma histamine concentration in any group.

Conclusions and Clinical Relevance—Hydromorphone is comparable to oxymorphone for preanesthetic sedation in dogs. Sedation is enhanced by acepromazine. Neither hydromorphone nor oxymorphone caused an increase in plasma histamine concentration. (*J Am Vet Med Assoc* 2001;218:1101–1105)

Opioids are used commonly in veterinary medicine for preanesthetic sedation and analgesia in dogs and other species. Opioids are generally classified by their receptor activity as pure agonist, partial agonist, mixed agonist-antagonist, or pure antagonist drugs.[1] Morphine, a pure agonist opioid, is the standard with which all other opioids are compared regarding receptor affinity and clinical effects. The pure agonist opioids induce dose-dependent sedation and analgesia in dogs. This class of opioids is also associated with bradycardia, respiratory depression, vomition, defecation, ileus, urinary retention, alterations in thermoregulation, and, occasionally, untoward excitement in dogs.[2] Some opioids, particularly morphine, induce histamine release from mast cells, which leads to vasodilation, urticaria, and decrease in blood pressure.[3,4] This effect is most profound when high doses of morphine are used or when the drug is given IV.

The use of opioids for sedation prior to general anesthesia or for chemical restraint during diagnostic or minor surgical procedures in dogs has been well-documented.[5-8] The quality of sedation in dogs is enhanced when opioids are combined with tranquilizers such as acepromazine.[5]

Oxymorphone is a pure agonist opioid with a receptor affinity approximately 10 times greater than morphine. Oxymorphone (0.05 to 0.2 mg/kg [0.02 to 0.09 mg/lb] of body weight) is quite effective for sedation in dogs, especially when combined with acepromazine (0.05 to 0.1 mg/kg [0.02 to 0.5 mg/lb]).[6,7,9] In dogs, oxymorphone may cause bradycardia, second-degree heart block, mild respiratory depression, vomition, defecation, auditory hypersensitivity, and panting. In healthy dogs, these effects are usually not detrimental; however, panting and auditory hypersensitivity may complicate the successful completion of diagnostic procedures. In contrast to morphine, oxymorphone does not induce histamine release in dogs.[4] In the United States, oxymorphone is expensive, and it has become increasingly difficult to locate commercially available stocks of the drug for purchase by veterinarians.[a]

Hydromorphone is also a pure agonist opioid, with a receptor affinity that is approximately 5 times that of morphine or half that of oxymorphone.[1] It is more widely used in human anesthesia than oxymorphone and, therefore, is more amply available from commercial sources. Hydromorphone is also less expensive than oxymorphone.[a]

To the authors' knowledge, no scientific data are available on the sedative properties or physiologic effects of hydromorphone in dogs. Although hydromorphone has been recommended for use in dogs, the comparative sedative and physiologic effects and effects on histamine release have not been scientifically documented.[10] The purposes of the study reported here were to compare hydromorphone with oxymor-

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Supported in part by the Companion Animal Foundation and the Department of Surgical Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, Wis.

Results of this study were presented in abstract form at the 1999 meeting of the American College of Veterinary Anesthesiologists, Dallas, Tex.

The authors thank Jennifer Blum for technical assistance.

phone, with or without acepromazine, for preanesthetic sedation in dogs and assess changes in plasma histamine concentration after drug administration.

Materials and Methods

Dogs—Ten male mixed-breed dogs that were judged healthy on the basis of physical examination findings, CBC, and results of serum biochemical analyses were used. Dogs were housed in pairs and given access to food and water ad libitum throughout the study. Dogs were accustomed to human contact and gentle restraint. The study was approved by the Research Animal Care and Use Committee of the University of Wisconsin. Mean ± SD age of the dogs was 1.07 ± 0.19 years, and body weight was 21.62 ± 1.54 kg (47.6 ± 3.4 lb).

Study design—Four treatments were tested in each dog in a randomized Latin-square design, with at least 7 days between treatments. Treatments were administered IM as follows: group H received hydromorphone[b] (0.22 mg/kg [0.1 mg/lb]), group O received oxymorphone[c] (0.11 mg/kg [0.05 mg/lb]), group H/A received hydromorphone (0.22 mg/kg) with acepromazine (0.05 mg/kg), and group O/A received oxymorphone (0.11 mg/kg) with acepromazine (0.05 mg/kg). All treatments were administered IM via a syringe wrapped in foil by a person who was not involved in scoring sedation or physiologic effects of the treatments.

Sedative effects—A single individual who was unaware of treatments and familiar with the dogs' normal behaviors was responsible for assessing sedative and physiologic effects of the treatments. Each dog was removed from its normal housing and acclimated to a small quiet room and ambient light for at least 30 minutes prior to treatment. During acclimatization and data collection, dogs were loosely restrained with a leash. After this acclimatization period, a baseline sedation score was assigned by use of a standardized sedation scoring system (**Appendix**). One of the 4 treatments was then administered, and sedation score was recorded at **time of administration (T0)** and at 5-minute intervals until **25 minutes after administration (T25)**. In addition, vomition or defecation, time to sitting, time to sternal recumbency, and any subjective adverse effects of treatment (eg, excitement, aggression) were recorded during this time. Time to sitting and time to sternal recumbency were defined as the number of minutes after T0 at which the dog first sat or became sternal and did not rise again to a standing position during the remaining time of observation. After measurements at T25, dogs were returned to a holding cage in a separate room for periodic observation until the end of the day, at which time they were placed in their normal housing environment.

Physiologic effects—Prior to baseline evaluation for sedation, dogs were instrumented with a pulse oximeter probe[d] placed on the lip and a Doppler ultrasonic flow probe placed above the carpus on the palmar digital artery with a sphygmomanometer and cuff (50% width of the antebrachium).[e] Heart rate, respiratory rate, **pulse oximetry oxygen saturation (SpO_2)**, and **systolic blood pressure (SBP)** were recorded every 5 minutes from T0 through T25. Heart rate was counted from the amplified Doppler flow probe during a 1-minute period. Respiratory rate was determined by observation.

Measurement of plasma histamine concentration—Immediately prior to treatment and at T25 after treatment, 5 ml of blood was aseptically collected from the lateral saphenous vein into chilled tubes that contained sodium EDTA as an anticoagulant. Tubes were immediately placed on ice. Within 2 hours, tubes were centrifuged for 10 minutes at 900 × g at 4 C. Plasma was aspirated and frozen at –70 C for later batch analysis. Histamine concentration (nanograms per milliliter of plasma) was determined by use of an enzyme immunoassay kit.[f] This assay has a sensitivity of 0.02 ng/ml, an interassay variability of approximately 12.5%, and cross-reactivity with multiple other histamine analogues of < 4%.

Statistical analyses—Times to initial sedation, sitting, and sternal recumbency were analyzed by use of a 1-way repeated measures ANOVA. Differences among groups and treatment across time effects in sedation scores were analyzed by use of the Kruskall-Wallis test for nonparametric data. Differences in heart rate, respiratory rate, SpO_2, and SBP from baseline to T25 for each treatment and for treatments across time were also analyzed, using the Kruskall-Wallis test.

The percentage of dogs in each treatment group that vomited, defecated, or panted at each time point was calculated, and differences in prevalence among treatments were analyzed by use of the Fisher exact test. Within each treatment, differences in plasma histamine concentration (before vs after drug administration) were analyzed by use of a 2-sample *t*-test. Comparisons among treatments for histamine concentrations were analyzed by use of a 1-way repeated measures ANOVA. For all tests, a value of $P < 0.05$ was considered significant.

Results

The maximum achievable sedation score, determined on the basis of our scoring system, was 14. Sedation scores were significantly higher from T10 to T25 in groups H/A and O/A, compared with groups H and O (**Fig 1**). At no time from T0 to T25 was there a significant difference in sedation score between groups H/A and O/A, or between groups H and O. Sedation scores in groups H/A and O/A at T25 approached the maximum possible score.

Mean ± SD times to initial sedation (ie, sedation score significantly different than baseline) for groups H, O, H/A, and O/A were 5.44 ± 0.86, 4.68 ± 0.81, 3.49 ± 0.49, and 3.70 ± 0.38 minutes, respectively. Differences among groups were not significant. There was no significant difference among groups in time to sitting or time to sternal recumbency.

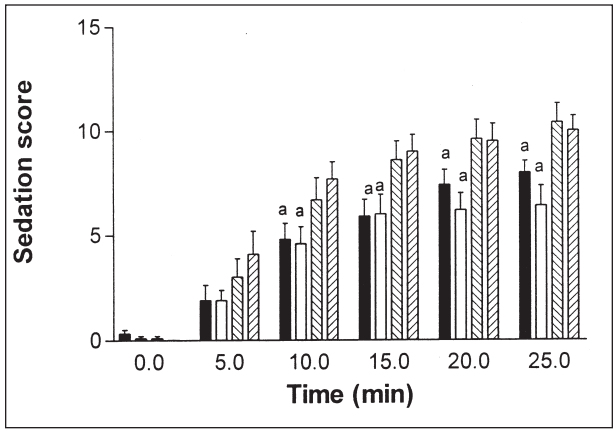

Figure 1—Mean ± SEM sedation scores determined at various times after administration of hydromorphone (solid bar), oxymorphone (open bar), hydromorphone and acepromazine (diagonally striped bar), or oxymorphone and acepromazine (diagonally striped bar). a = Significantly ($P < 0.05$) different from hydromorphone-acepromazine and oxymorphone-acepromazine.

There were no significant differences among time points within treatment groups with respect to SBP. Differences between certain treatment groups in SBP at T25 were detected; SBP was significantly lower at T25 in group H/A (140.9 ± 7.9 mm Hg), compared with group H (158.9 ± 9.7 mm Hg), and in group O/A (148.5 ± 8.6 mm Hg), compared with group O (166.0 ± 7.2 mm Hg).

There were no significant differences in heart rate among treatment groups at each time point. In all treatment groups, heart rate at T25 was significantly decreased, compared with heart rate at T0 (**Fig 2**). However, heart rates in all dogs remained within clinically acceptable limits at T25.

The number of dogs that panted was significantly greater in group O at T5 and T10, compared with the other 3 groups (**Fig 3**). From T15 to T25, prevalence of panting was equivalent in groups H and O and was significantly greater than in groups H/A and O/A.

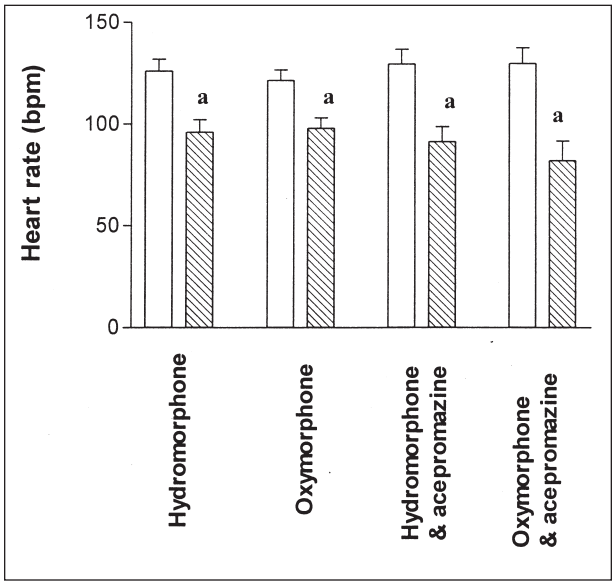

Figure 2—Mean ± SEM heart rate (beats per minute [bpm]) determined immediately after drug administration (open bars) and 25 minutes after drug administration (striped bars) in dogs that received various sedatives. a = Significantly ($P < 0.05$) different from value obtained immediately after drug administration.

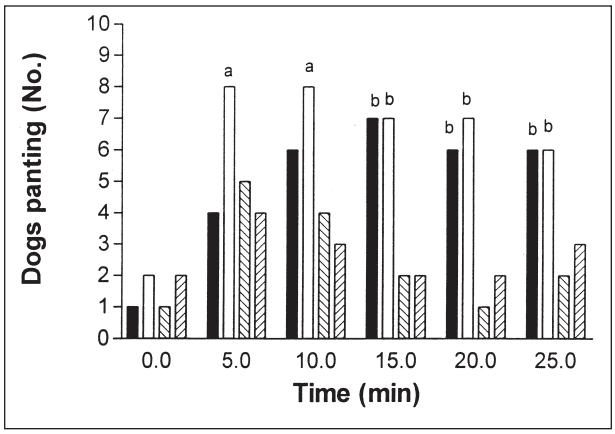

Figure 3—No. of dogs (n = 10/group) that panted at various times after administration of hydromorphone (solid bar graphic), oxymorphone (open bar graphic), hydromorphone and acepromazine (diagonally striped bar graphic), or oxymorphone and acepromazine (diagonally striped bar graphic). a = Significantly ($P < 0.05$) different from the other 3 drugs. b = Significantly ($P < 0.05$) different from oxymorphone-acepromazine and hydromorphone-acepromazine.

Significant differences in SpO_2 were not detected at any time point either within groups or among groups. The SpO_2 values remained > 90% in all dogs at all times. Neither vomition nor defecation occurred in any dog after any of the 4 treatments, and other adverse effects were not detected.

For all groups, mean ± SD plasma histamine concentration was 1.72 ± 2.69 ng/ml at baseline and 1.13 ± 1.18 ng/ml at T25. Plasma histamine concentrations for each group did not change significantly from baseline to T25.

Discussion

The receptor affinity of hydromorphone is approximately 5 times greater than morphine[11]; thus, it follows that a dose one fifth that of a standard morphine dose would be clinically applicable. In dogs, the recommended dose range for morphine when used as a preanesthetic sedative is 0.5 to 1.0 mg/kg.[8] Thus, we chose a dose of 0.22 mg/kg for hydromorphone. Because oxymorphone has a receptor affinity 10 times greater than that of morphine, commonly accepted doses for oxymorphone are 0.05 to 0.1 mg/kg. The dose of acepromazine chosen in our study was similar to that of other studies[6,7]; however, in those studies, acepromazine was administered IV. The effect of higher doses of acepromazine (1.0 mg/kg) alone have been studied after IM administration in dogs.[12] However, much lower doses of acepromazine are effective for sedation without causing profound decreases in blood pressure.[5] Thus, we chose a conservative dose of acepromazine that would mimic a clinical situation in which one may administer acepromazine in combination with an opioid to a healthy dog as a preanesthetic sedative. We also chose to administer all treatments IM in order to best represent a clinical situation in which IV administration of preanesthetic medications may cause undue stress to the dog.

Results of our study suggest that hydromorphone is equally as effective as oxymorphone for sedation in healthy dogs. When hydromorphone is combined with acepromazine for neuroleptanalgesia, the degree of sedation is enhanced considerably. These findings are similar for oxymorphone in combination with acepromazine.[6,7,13] All dogs were in sternal recumbency within 20 minutes of receiving all 4 treatments. At T25, all dogs in all 4 groups were tractable and easily restrainable for venous blood sampling.

Heart rate commonly decreases within 10 minutes of opioid administration in dogs.[13-15] In our study, heart rates decreased significantly by T25 as a result of administration of opioid and opioid-acepromazine combinations. Decrease in heart rate was not significantly different among treatments. Decrease in heart rate after oxymorphone administration is attributed to centrally mediated increases in vagal tone[16]; this is presumably also the mechanism by which hydromorphone causes decreased heart rate. Second-degree atrioventricular block has also been reported after oxy-

morphone administration. In our study, rhythm was assessed by listening to the Doppler probe as it amplified pulses in the dorsal pedal artery; ECG tracings were not recorded. Arrhythmias were not detected in any dog after any of the 4 treatments; however, we cannot rule out the possibility that a regular nonsinus rhythm may have been present in some dogs. The degree of bradycardia detected in this study was less than that reported by some authors.[16] This is likely attributable to the fact that IM administration of the drugs resulted in lower peak plasma concentrations.

In general, opioids have little effect on blood pressure in healthy dogs.[7,17] When acepromazine is given alone or in combination with oxymorphone, blood pressure decreases significantly.[7,12,17] In the study reported here, we observed mild but significant decreases in SBP at T25 in dogs that received acepromazine with oxymorphone or hydromorphone. This was likely attributable to α-antagonist properties of acepromazine, which caused vasodilation.[18] However, at the dose of acepromazine used in our study, in combination with oxymorphone or hydromorphone, SBP remained well within clinically acceptable limits in all dogs.

Panting has been reported as a frequent occurrence after oxymorphone administration.[6] This is thought to be attributable to an opioid effect on the thermoregulatory center. When combined with acepromazine, prevalence of panting after administration of oxymorphone is diminished.[7] Our results with hydromorphone were similar. However, we did observe that prevalence of panting prior to peak sedation was greater in dogs treated with oxymorphone, compared with those treated with hydromorphone. The addition of acepromazine to hydromorphone or oxymorphone resulted in decreased panting at most time points. In the study reported here, respiratory depression after opioid administration was not evaluated. Hemoglobin saturation remained within acceptable limits in all dogs (breathing room air) despite panting in some dogs.

Vomition and defecation have been reported after administration of oxymorphone and acepromazine in dogs.[6] Vomition, defecation, nausea, vocalization, or excitement were not detected in any dog after any treatment in our study. Food had not been withheld from dogs in our study, and it seemed unlikely that food in the stomach would cause the dogs to be less likely to vomit. Dyson et al[6] reported excitement (36%), vocalization (28%), and defecation (12%) after sedation was induced by use of oxymorphone and acepromazine in dogs. It is possible that prevalence of these adverse effects was so low that they were not observed because of the small number of dogs in each of our groups.

In an in vitro model that used porcine mast cells, neither morphine nor hydromorphone at high concentrations induced substantial histamine release.[19] However, increases in plasma histamine concentration after morphine, but not oxymorphone, administration in dogs have been documented.[4] These results are consistent with results of similar studies in humans.[20] In in vivo[4,20] and in vitro[19] studies, histamine release from human mast cells is significantly increased by 10 minutes after morphine administration. In our study, significant increases were not detected in plasma histamine concentration after administration of either oxymorphone or hydromorphone alone or when either opioid was combined with acepromazine. In our study, it was expected that plasma concentrations of drugs administered IM peaked by 20 minutes after administration and that any effects of the drugs on release of histamine from mast cells occurred within the 25-minute observation period. All dogs had baseline histamine concentrations that were within the range reported in the literature.[4,21] The assay used for plasma histamine concentration in our study is a verified method.[22] It is possible that IV administration of hydromorphone could induce histamine release from mast cells. Therefore, until proven otherwise, hydromorphone should be administered IV with caution and with concurrent monitoring of blood pressure.

Results of our study suggest that hydromorphone is a safe and effective opioid when used for preanesthetic sedation in healthy dogs. Sedation with hydromorphone may be enhanced by administration of acepromazine. It is possible that we missed peak sedation from our drug treatments, because we followed sedative and physiologic effects for only 25 minutes after drug administration. Results suggested that sedation had reached a plateau in 25 minutes only in the group that received oxymorphone. When acepromazine is given IM to dogs, maximum sedative effects develop in 30 to 45 minutes.[5] However, in all dogs in our study, sedation scores at 25 minutes after drug administration approached the maximum score, and if additional sedation did develop during the period after we discontinued recording data, it is unlikely to have been substantially greater.

Overall, the 4 treatments administered to dogs in our study were quite effective as preanesthetic sedatives. By 25 minutes after drug administration, all dogs in all treatment groups had achieved sufficient sedation for restraint and IV catheter placement. At the doses used in the study reported here, hydromorphone, like oxymorphone, appears to cause mild bradycardia and will cause approximately 60% of dogs to pant by 20 to 25 minutes after administration. Clinically, hydromorphone appears to be equivalent to oxymorphone for use in dogs as a preanesthetic sedative. Additionally, hydromorphone may be a more cost-effective and convenient opioid than oxymorphone in veterinary practice.

[a]Bindley Western Wholesaler, Atlanta, Ga.
[b]Hydromorphone injection USP, Elkins-Sinn, Cherry Hill, NJ.
[c]Numorphan, Endo Pharmaceuticals Inc, Chadds Ford, Pa.
[d]Surgivet pulse oximeter, Surgivet, Waukesha, Wis.
[e]Ultrasonic Doppler, Parks Electronics, Aloha, Ore.
[f]Histamine immunoassay, Immunotech, Beckman Coulter Inc, Palatine, Ill.

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Appendix

Sedation scoring system used to evaluate effects of hydromorphone and oxymorphone, with or without acepromazine, on preanesthetic sedation in dogs

Observation	Score	Criteria
Vocalization	0	Quiet
	–1	Whining softly but quiets with soothing touch
	–2	Whining continuously
	–3	Barking continuously
Posture	3	Lateral recumbency
	2	Sternal recumbency
	1	Sitting or ataxic
	0	Standing
	–1	Continuous movement
Appearance	3	Eyes sunken, glazed, unfocused, ventromedial rotation
	2	Eyes glazed but follow movement
	1	Nictitating membrane protruded; normal visual responses
	0	Normal appearance
	–1	Pupils dilated; abnormal facial expression
Interactive behaviors	3	Recumbent; no response to voice or touch
	2	Recumbent; lifts head in response to voice or touch
	1	Recumbent but rises in response to voice or touch
	0	Standing or sitting up; normal response to voice or touch
	–1	Moves away from voice or touch; "jumpy"
	–2	Growls/hisses when approached or touched
	–3	Bites/swats when approached
Restrainability	2	Lies on floor with minimal restraint needed
	1	Lies on floor with light restraint of head/neck
	0	Sits up on floor; attempts to jump despite restraint
	–1	Struggles against restraint continuously
	–2	Cannot be restrained for > 20 seconds
Noise response	3	No response to a hand clap near the head
	2	Minimal response to a hand clap near head
	1	Slow/moderate response to hand clap near head
	0	Brisk response to a hand clap; raises head, eyes open.
Analgesia	2	No response to needle prick of foot pad
	1	Slowly pulls limb away in response to needle prick
	0	Briskly pulls limb away in response to needle prick
	–1	Pulls limb away and growls when needle touches skin
	–2	Pulls limb away before needle touches skin