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A comparison of the effects of hydromorphone HCl and a novel extended release hydromorphone on arterial blood gas values in conscious healthy dogs

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Abstract

The purpose of this study was to evaluate arterial blood gases in dogs that were given hydromorphone or extended release liposome-encapsulated hydromorphone (LEH). Dogs were randomly administered LEH, $n = 6$, (2.0 mg kg^{-1}), hydromorphone, $n = 6$, (0.2 mg kg^{-1}) or a placebo of blank liposomes, $n = 3$, subcutaneously on separate occasions. Arterial blood samples were drawn at serial time points over a 6-h time period for blood gas analysis. There was no change from baseline values in $P_a\text{CO}_2$, $P_a\text{O}_2$, (HCO_3^-), pH, and SBEC in the dogs that received the placebo. Administration of hydromorphone resulted in significant increases in $P_a\text{CO}_2$ (maximum (mean + SD) $44.4 + 1.1 \text{ mm of Hg}$) and significant decreases in $P_a\text{CO}_2$ (minimum (mean + SD) $82.4 + 4.7 \text{ mm of Hg}$) and pH (minimum (mean + SD) $7.31 + 0.01$) compared with baseline. Administration of LEH resulted in significant increases in $P_a\text{CO}_2$ (maximum (mean + SD) $44.6 + 0.9 \text{ mm of Hg}$) and significant decreases in $P_a\text{O}_2$ (minimum (mean + SD) $84.8 + 2.6 \text{ mm of Hg}$) and pH (minimum (mean + SD) $7.34 + 0.02$) compared with baseline. There was no significant difference between these two groups at any time point. The changes observed in $P_a\text{CO}_2$, $P_a\text{O}_2$, and pH, however, were within clinically acceptable limits for healthy dogs. LEH was determined to cause moderate changes in arterial blood gas values similar to those caused by hydromorphone.

Keywords

Hydromorphone; Extended release; Liposome; Dog; Hypercapnia; Hypoxemia

1. Introduction

In veterinary medicine today there are few options for fully effective and safe analgesic drugs for companion animals, although opioids remain the cornerstone for management of both acute and chronic pain. There are currently several classes of drugs, including opioids, commercially available for analgesia, although not all are FDA approved for dogs. Of the available analgesics, opioids have been shown to offer the most reliable, effective analgesia for acute pain management and perioperative analgesia (Pascoe, 2000). In dogs, behavioral side effects of opioids, particularly hydromorphone, include panting, vocalization,

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salivation, nausea, vomiting, defecation, and sedation or hyperactivity (Kukanich et al., 2008a). Physiologic side effects of opioids in dogs may include CNS depression, respiratory depression, bradycardia, usually accompanied with little to no change in cardiac output, ileus, and urinary retention (Wagner, 2002). In humans, the most feared side effect of opioids in the perioperative setting is respiratory depression (Dahan, 2007).

Controversy exists among researchers and veterinary clinicians as to the degree of respiratory depression that occurs with opioids in dogs. In general, respiratory depression is thought to be dosedependent, becoming more extreme with higher opioid doses (McKelvey and Hollingshead, 1994). In one study of relatively high doses of IV oxymorphone in dogs, mild hypercapnia and hypoxemia were reported, with the most significant effects occurring 5–10 min after drug administration (Copeland et al., 1987). A second study comparing butorphanol and hydromorphone post-operatively in dogs after ovariohysterectomy or castration reported mild hypercapnia and hypoxemia from 30 min to 2 h after extubation in dogs that received hydromorphone, but no significant change in P_aCO_2 in dogs that received butorphanol (Campbell et al., 2003). Another study reported limited respiratory depression with sufentanil in dogs, although at a dose of 12 $\mu\text{g kg}^{-1}$ IV mean P_aCO_2 approached 52.5 ± 5.0 mm of Hg and mean P_aO_2 approached 55 ± 7.0 mm of Hg (Freye et al., 2000). Although these studies reported changes in arterial blood gases that would suggest minimal respiratory depression after clinically relevant doses of opioids in healthy dogs, it is important to take into account that the drug(s) in question must be given fairly often in order to maintain an analgesic effect (Kukanich et al., 2008a,b). This means that respiratory depression, if present, will occur with each bolus dose of opioid and may substantially affect oxygenation and acid–base balance sequentially during the course of treatment.

A novel formulation of extended release hydromorphone utilizes a liposome encapsulation technique composed of dipalmitoylphosphatidylcholine and cholesterol and made with freeze-thaw methods to allow the opioid to be released gradually over time from the liposome (Smith et al., 2004, 2008). Our laboratory recently reported that this formulation of extended release hydromorphone (LEH) provides theoretically analgesic serum concentrations of drug in healthy dogs for up to four days after a single dose (Smith et al., 2008). In general, LEH must be dosed in mg kg^{-1} at 10 times the dose of the comparable standard preparation in order to allow for the reservoir of drug stored within the liposome that is continually released. Therefore, we were interested in whether this extended release preparation would cause more profound respiratory depression than a comparable dose of the standard, short-acting drug.

The purpose of the study reported here was to compare changes in arterial blood gas values in healthy dogs breathing room air after they received either hydromorphone HCl or LEH. Because we have shown that LEH produces relatively steady state serum concentrations of hydromorphone, we hypothesized that changes in arterial blood gas values would be less than, or comparable to, those seen after dogs were administered the standard drug.

2. Materials and methods

Six male neutered beagles, ranging in age from 12.37 to 14.25 months and weighing 10.98 to 12.4 kg, were used for data collection. Dogs were purpose-bred and obtained from a commercial source (Ridglan Labs, Mount Horeb, WI, USA). All dogs were judged to be healthy based on physical exam, complete blood counts and serum chemistry profiles obtained prior to being entered in the study. The study was approved by the University of Wisconsin Animal Care and Use Committee and adhered to all USDA and AALAS guidelines for the use of animals in research. The dogs were fasted for 8–12 h prior to data collection but had ad lib access to water during this time. Dogs were weighed on each day of the study to ensure accurate dosing on a mg kg^{-1} basis.

On the morning of study a 20 gauge $\times$ 1¼ in. sterile catheter (Terumo, Somerset NJ, USA) was placed and secured in a cephalic vein. Each dog was then anesthetized with propofol (Propoflo, Abbott Animal Health, North Chicago, IL, USA) (10 mg ml^{-1}), given intravenously to effect via the cephalic catheter. Dogs' tracheas were intubated and the lungs ventilated as needed by an assistant using an Ambu bag. A 20 gauge $\times$ 1 ¼in. sterile catheter was aseptically placed and secured in the dorsal pedal artery of the left hind limb. A second 22 gauge $\times$ 8 in. silastic catheter (Intracath, Abbott Laboratories, Abbott Park, IL, USA) was then threaded through the 20 gauge catheter in order to be able to obtain blood samples from a central artery. In each dog, the 8 in. catheter was threaded the entire length, so the proximal end was located at approximately the same place within the femoral/caudal aortic artery in all dogs, due to the relatively uniform size of the dogs used in this study. The distal end was capped with a standard injection port. Arterial catheters were held in place with skin staples. The entire procedure for placing the arterial catheter took less than 15 min or the experiment was aborted for the day. After placement of the arterial catheter, dogs were allowed to recover from anesthesia. The dogs' tracheas were extubated when an obvious gag reflex was observed. At least 30 min elapsed from the last propofol injection before arterial blood sampling began. During the 6 h period of arterial blood gas sampling, dogs were positioned in sternal recumbency, or rolled from right to left lateral recumbency, while they were sedate from the opioid. At later time points, or in the case of the placebo treatment, when dogs were not sedate they were allowed to roam freely about the laboratory except while samples were being obtained, during which time they were gently restrained. Therefore it is unlikely that significant atelectasis occurred in these dogs over the course of the experimental day.

All arterial samples were obtained in a 3 ml syringe that had been washed with 1000 IU ml^{-1} heparin (Heparin, Cardinal Laboratories, Hudson, WI, USA) attached to a 22 gauge needle. For purposes of arterial blood sampling, the catheter was first flushed with 2 ml of 10 IU ml^{-1} heparinized saline (Hospira Inc., Lake Forest, IL, USA), then 4 ml of heparinized saline/blood was withdrawn and set aside. A 1 ml sample of arterial blood was anaerobically collected over a 30 s time period, all gas bubbles were ejected via the needle, and the sample was immediately placed on ice. Needles were replaced with airtight plastic caps. The 4 ml of heparinized saline was then reinjected and a second flush of 2 ml of 10 IU ml^{-1} heparinized saline was administered. No arterial blood samples were held on ice for longer than 45 min.

A baseline arterial sample was collected from each dog and immediately analyzed to ensure that there were no residual respiratory effects present from the propofol and that all values were within normal limits for a conscious dog breathing room air (21% oxygen at a barometric pressure of 1 atm). At that time, treatments were randomized such that each dog received (a) a subcutaneous injection of hydromorphone HCl at 0.2 mg kg^{-1} ; (b) a subcutaneous injection of LEH at 2.0 mg kg^{-1} ; or (c) a subcutaneous injection of blank liposomes (placebo) at 1.5 ml dog^{-1} . Treatment randomization was determined by randomization software (RandomBots Medusa, RandomBots, Long Beach, CA, USA). Each dog ($n = 6$) received both hydromorphone HCl and the liposome-encapsulated formulation of hydromorphone (LEH) with a minimum two week washout period between treatments. Three dogs also received a placebo, liposomes filled with acetate buffer, as negative controls, again with a minimum two week washout period between treatments. Hydromorphone HCl was obtained from a commercial source (Hospira Inc., Lake Forest, IL, USA). LEH and liposomes containing acetate buffer were synthesized in our laboratory using a method that has been described (Smith et al., 2008). Arterial blood samples were obtained at 0 (baseline), 5, 10, 15, 30, 45, 60, and 90 min and 2, 4, and 6 h after drug or placebo injection. Rectal temperature was measured using a digital thermometer during the time of arterial sample collection at each time point in order to temperature correct the sample at analysis. Following the 6 h blood sample collection, both the cephalic and arterial catheters were removed and the sites were gently wrapped with 4×4 gauze and Vetwrap (Vetwrap, 3M Corporation, Saint Paul, MN, USA).

Blood samples were analyzed using an ABL Radiometer 500 (Radiometer Ltd., Crawley, West Sussex, UK). This device gives values for PCO_2 , PO_2 , HCO_3^- , pH, and SBEc (base excess). Data were tested for normal distribution using the Shapiro–Wilk test. Paired Student t-tests were used to compare data within a group to baseline values and unpaired Student t-tests were used to compare data at each time point between groups (Systat®, Systat Software Inc., San Jose, CA, USA).

3. Results

There was no significant difference between groups in the dose of propofol required for intubation ($6.0 \pm 2.1 \text{ mg kg}^{-1}$) or the total dose of propofol administered during the period of arterial catheter placement ($56.3 \pm 10.1 \text{ mg}$). All dogs that received either hydromorphone HCl or LEH showed moderate sedation from 15 min to 3 h after drug administration. This sedation was characterized by either sternal or lateral recumbency, but arousable with voice or touch, and mild ataxia when walking. Some dogs also vomited, defecated, salivated, panted, and/or vocalized after treatment. In this study we did not record sedation or incidence of other side effects, such as vomiting, but this information has been published by our laboratory in pharmacokinetic studies of hydromorphone HCl and LEH in beagle dogs of similar age and weight (Kukanich et al., 2008a; Smith et al., 2008). In this study, one dog in the placebo group panted from baseline to 1 h after treatment, two dogs in the LEH group panted from 5 min to 2 h after treatment, and 3 dogs in the hydromorphone HCl group panted from 15 min to 1 h after treatment.

Ambient temperature was kept constant throughout the study. For the placebo group, rectal temperatures ranged (min–max) from 99.2 to 101.8 °F; for the hydromorphone group, rectal temperatures ranged (min–max) from 96.4–102.0 °F; for the LEH group, rectal temperatures ranged (min–max) from 97.2–101.1 °F. Temperatures tended to trend down in both groups that received a form of hydromorphone and temperatures trended up in the placebo group, but these changes were not statistically significant.

A relatively large variability in baseline P_aO_2 was observed in this study. This was due to one dog in the placebo group that had a baseline P_aO_2 of 85.00 mm of Hg and one dog in the LEH group that had a baseline P_aO_2 of 106.30 mm of Hg. There was no significant difference in P_aO_2 in the placebo group at any time point compared to baseline values. A decrease in P_aO_2 was detected after treatment with LEH and with hydromorphone HCl (Fig. 1). In dogs receiving LEH, the decrease was greatest from 20–90 min post-injection, with P_aO_2 values in mm of Hg (mean + SD) equal to 86.77 ± 1.72 , 86.85 ± 1.65 , 85.27 ± 4.72 , 84.75 ± 2.62 , and 88.05 ± 5.17 , respectively. When compared to the placebo group, these decreases were statistically significant from 20 to 90 min after drug administration. A similar decrease in P_aO_2 was observed after treatment with hydromorphone HCl, with statistically significant differences when compared with the placebo group from 10 to 45 min post-injection (Fig. 1). In the hydromorphone HCl group from 10–45 min post-injection, P_aO_2 values in mm of Hg (mean + SD) were 87.00 ± 3.07 , 83.17 ± 0.67 , 82.35 ± 4.72 , and 86.77 ± 2.02 , respectively. When compared to baseline values for P_aO_2 , hydromorphone HCl resulted in significantly lower values from 10 to 45 min and LEH at 30, 60, and 120 min after drug administration. When values were compared between hydromorphone HCl and LEH, there were no statistically significant differences at any time point during the 6 h of data collection (Fig. 1). No dog in either of the treatment groups for either formulation of hydromorphone had a P_aO_2 value <75.98 mm of Hg at any time point.

There was no change in P_aCO_2 at any time point compared to baseline in the placebo treated group. Treatment with either hydromorphone HCl or LEH caused an increase in P_aCO_2 values (Fig. 2). Both treatments produced results that closely paralleled each other, with significant increases in P_aCO_2 , when compared to baseline values, after LEH from 10 to 30 min and from 45 to 120 min post-injection in mm of Hg (mean + SD) of 42.67 ± 0.30 , 44.55 ± 0.90 , 43.87 ± 0.67 , 43.35 ± 0.67 , respectively; and after hydromorphone HCl from 30 to 120 min post-injection in mm of Hg (mean + SD) of 42.07 ± 1.57 , 44.40 ± 1.12 , 44.10 ± 1.27 , 43.95 ± 1.12 , respectively. P_aCO_2 values remained slightly elevated out to 360 min (40.20 ± 1.12 for LEH and 39.00 ± 1.50 for hydromorphone HCl), but at 6 h these differences were not significantly different from baseline values within the group. There was no statistically significant difference in P_aCO_2 between hydromorphone HCl and LEH at any time point. A comparison between LEH and the placebo treatment showed statistical significance between 20 and 120 min, with p -values ≤ 0.001 (Fig. 2). At 240 min there was no significant difference in P_aCO_2 between the LEH group and the placebo control, but at 360 min the difference was again statistically significant ($p < 0.006$). A comparison of hydromorphone HCl and the blank liposomes control showed statistical significance between 30 and 120 min, with p -values ≤ 0.006 .

pH values were decreased with both forms of hydromorphone, but more so for treatment with standard hydromorphone (Fig. 3). pH reached a minimum at 60 min post-injection for hydromorphone HCl (7.314 ± 0.004) and 90 min post-injection for LEH (7.343 ± 0.021). There was no difference at any time point in pH between the hydromorphone HCl group and the LEH group. There was no statistically significant difference between baseline pH and pH at any time point after drug administration in the LEH group, nor was there any significant difference at any time point between LEH and the placebo control group. However, when compared with the placebo control group, pH in the hydromorphone HCl group was significantly lower between 20 and 240 min after drug administration (Fig. 3).

Values for (HCO_3^-) were increased after treatment with either hydromorphone HCl or LEH (data not shown). None of the observed increases in (HCO_3^-) were statistically significant when the treatment groups were compared at each time point or within treatment group compared to baseline.

4. Discussion

Opioids are currently the most effective analgesics available in human and veterinary medicine. The parenteral route of opioid administration ensures drug delivery to CNS opioid receptors and is the most appropriate route for acute perioperative pain. Generally, parenteral administration results in transient high serum concentrations of drug that will be associated with more adverse drug effects, with a relatively quick decline in serum concentrations and a waning of their analgesic and adverse effects. In the study reported here, we found that both hydromorphone HCl and an extended release preparation of hydromorphone, LEH, produced modest hypoxemia and hypercapnia in healthy dogs breathing room air. These changes persisted through the 6 h sampling time period, but were within clinically acceptable limits for healthy dogs and were not associated with any untoward outcomes. Although the number of dogs in each group ($n = 6$ in the 2 hydromorphone test groups and $n = 3$ in the placebo group) to some degree limits the power of this study, the variances were similar between groups and the data generated with respect to changes in P_aCO_2 and P_aO_2 were similar to those reported in the literature after hydromorphone in healthy dogs (Campbell et al., 2003). In this study we also observed variability in baseline P_aO_2 . While this variability is noteworthy, it is compatible with data found in the literature, where ranges for normal P_aO_2 in unanesthetized dogs breathing room air have been reported as 81.60–101.50 mm of Hg (Feigl and D'Alecy, 1972). All dogs had normal physical exams and thoracic auscultation, although we did not perform pre-study thoracic radiographs or other diagnostics to rule out subclinical respiratory disease. At baseline, all dogs were actively moving around the lab just prior to sample collection, so it is unlikely that atelectasis had occurred at that time point.

In the human literature, respiratory depression from opioids is considered the most dangerous adverse effect (Dahan, 2007). One study reported that respiratory depression occurs in 0.3–17% of all human post-operative patients taking opioids for pain (Cashman and Dolin, 2004). Fatal respiratory depression is usually the cause of death in accidental opioid overdose in humans (White and Irvine, 1999; Lotsch et al., 2006). Equianalgesic doses of opioids result in comparable degrees of respiratory depression (Schug et al., 1992).

Human patients at increased risk for opioid-related respiratory depression may be those with advanced age, obesity, a history of sleep apnea, concurrent sedation, and renal or hepatic disease that might affect drug metabolism and clearance (Smith, 2007). Presumably, some of these same factors would apply to canine patients receiving perioperative opioids. Several other studies suggest that hydromorphone, and presumably other agonist opioid drugs, are relatively safe in humans with dyspnea or pain from cancer. One author reported that, while hydromorphone decreased respiratory rate and signs of dyspnea in patients with respiratory distress, carbon dioxide and oxygen levels (measured non-invasively) showed no changes from baseline (Clemens and Klaschik, 2008). In a population of geriatric cancer patients, no significant changes were seen in non-invasive measures of P_aO_2 or P_aCO_2 during a 2 month titration of oral morphine for pain relief (Estfan et al., 2007).

Agonist opioids, such as hydromorphone, shift the CO_2 ventilatory response curve to the right, such that higher arterial CO_2 levels are needed to stimulate an increase in ventilation. Respiratory depression would be indicated by a clinically significant increase in P_aCO_2 in conscious dogs that have received opioids. In dogs breathing room air at sea level (21% inspired oxygen concentration) hypoventilation can be associated with a concurrent decrease in P_aO_2 . There are relatively few reports in the veterinary literature of opioid-induced respiratory depression in dogs, and some clinicians debate the significance of respiratory depression from opioids in this species. Studies by Campbell and Copeland both reported mild decreases in P_aO_2 and increases in P_aCO_2 in dogs receiving oxymorphone or hydromorphone (Copeland et al., 1987; Campbell et al., 2003). Berg and Orton examined the changes in arterial blood gases and respiratory rates in dogs given either morphine, oxymorphone, saline, or an intercostal nerve block after thoracotomy and reported significant increases in P_aCO_2 and decreases in P_aO_2 in the two groups that received systemic opioids (Berg and Orton, 1986). However, the changes reported in P_aCO_2 , while significantly different from the control and intercostal block group and significantly higher than the normal values for the laboratory referenced in that study (barometric pressure 0.84 atm), were within what would normally be considered clinically acceptable in healthy dogs. The values for P_aO_2 reported in that study for dogs that received the 2 opioid treatments were approximately 20.0–25.0 mm of Hg lower than normal values and were sufficiently low to cause hemoglobin desaturation. One consideration in evaluating these data, however, is that thoracotomy can induce ventilation–perfusion mismatch and atelectasis, and this combined with hypoventilation in dogs breathing room air would explain this degree of hypoxemia. Other studies in dogs have reported mild respiratory depression after various agonist opioids, including sufentanil (Polis et al., 2006), and epidural or intramuscular oxymorphone (Vesal et al., 1996).

As might be expected, combinations of sedative drugs and hydromorphone cause a greater degree of respiratory depression and hypoxia in dogs breathing room air. A combination of medetomidine and hydromorphone, given IV, caused significant increases in P_aCO_2 and decreases in P_aO_2 , although the actual values were not considered clinically important (Kuo and Keegan, 2004). A second study reported more dramatic decreases in P_aO_2 , that could be considered clinically important (P_aO_2 75.8–79.9 mm of Hg), after dogs were given IV medetomidine and hydromorphone (Enouri et al., 2008).

Similar to other reports in the literature, results from the present study suggest that both hydromorphone HCl and LEH, an extended release preparation of this drug, cause some degree of respiratory depression, respiratory acidosis, and relative hypoxemia in healthy dogs. Overall, the degree of hypercapnia and hypoxemia observed in dogs that received LEH was comparable to that observed with hydromorphone HCl, a drug that has already been deemed safe and is very popular in veterinary medicine for pain management and preanesthetic sedation in dogs (Pettifer and Dyson, 2000; Smith et al., 2001). While there were some statistically significant differences at some time points between placebo-treated dogs and the 2 groups that received either hydromorphone HCl or LEH, values for P_aCO_2 , P_aO_2 , and pH remained within normal limits (Table 1). Because the dose of LEH administered was ten times the dose in $mg\ kg^{-1}$ of hydromorphone HCl, the possibility existed that some bolus release of drug from the liposome would be associated with much more severe respiratory depression. It appears, however, that the steady state pharmacokinetics and extended release nature of this preparation obviates concerns about bolus effects when the preparation is administered subcutaneously.

Only six dogs were used in this study to minimize animal use, but even with this number of animals we were able to show statistically significant differences between groups at some time points. It is unlikely that increasing the number of animals studied would have resulted in dramatically different findings. We did see a significant difference in P_aCO_2 between the placebo group and the LEH group at our 6 h time point, and, unfortunately we did not sample beyond that. The authors are not aware of any data in the literature that reports arterial blood gas values beyond 6 h in healthy dogs that have received hydromorphone. Again, the mean P_aCO_2 in the LEH group at 360 min was 43.40 ± 0.67 mm of Hg, a value that would be considered acceptable by most clinicians. Based on the pharmacokinetic data we have published on LEH, we know that by 6 h after LEH administration at $2.0\ mg\ kg^{-1}$ to dogs, serum concentrations (and presumably opioid receptor occupancy) has reached steady state conditions (Smith et al., 2008). Therefore, it would be unexpected that the arterial blood gas values observed in this group at 6 h would differ considerably at time points measured further out. These six dogs were also normal, healthy dogs with no pain and no surgical intervention potentially affecting ventilation. In humans, patients receiving opioids for actively painful conditions are less prone to respiratory depression than healthy volunteers (Estfan et al., 2007). Therefore, it could be anticipated that dogs receiving hydromorphone or LEH to treat pain might actually have less respiratory depression than the dogs observed in this study.

In conclusion, in healthy dogs, hydromorphone HCl and LEH cause equivalent changes in arterial carbon dioxide and oxygen tensions, with mild increases in P_aCO_2 and corresponding decreases in pH, and mild decreases in P_aO_2 . Based on normal blood gas values for our laboratory, these small changes would be considered within normal limits for dogs breathing an un-enriched oxygen mixture. In dogs with pulmonary disease, post-surgical dogs, or dogs with extra-thoracic disease that may inhibit ventilation, liposome-encapsulated hydromorphone and hydromorphone HCl may cause more dramatic changes in arterial blood gas values.

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Fig. 1.

Changes in P_aO_2 with time after treatment with blank liposomes, hydromorphone HCl, or LEH. Values are reported in mm of Hg. * denotes a value significantly different from baseline value within that group. # denotes a value significantly different from placebo at that time point.

Fig. 2.

Changes in P_aCO_2 with time after treatment with blank liposomes, hydromorphone HCl, or LEH. Values are reported in mm of Hg. * denotes a value significantly different from baseline value within that group. # denotes a value significantly different from placebo at that time point.

Fig. 3.

Changes in pH with time after treatment with blank liposomes, hydromorphone HCl, or LEH. * denotes a value significantly different from baseline value within that group. # denotes a value significantly different from placebo at that time point.

Table 1

Canine normal arterial blood gas levels.

Component	Normal value
pH	7.35–7.45
pCO ₂	35.02–45.00 mm of Hg
pO ₂	79.95–109.95 mm of Hg
(HCO ₃ [−])	25–35 mmol/L

From DC Plumb, (2005), Veterinary Drug Handbook, Blackwell Publishing Professional, Ames IA. 1245; and Fiegl et al. (1972).