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Analgesic Efficacy and Safety of Hydromorphone in Chinchillas (*Chinchilla lanigera*)

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Limited information is available regarding the efficacy of opioid analgesics in chinchillas. Here we sought to evaluate the analgesic efficacy and safety of hydromorphone in chinchillas. In a randomized, controlled, blind, complete crossover design, hydromorphone was administered at 0.5, 1, and 2 mg/kg SC to 16 chinchillas. Analgesic efficacy was determined by measuring hindlimb withdrawal latencies after a thermal noxious stimulus (Hargreaves method) at 0, 1, 2, 4, and 8 h after drug administration. Changes in daily food intake and fecal output after hydromorphone administration were recorded. At 2 mg/kg SC, but not at lower dosages, hydromorphone increased withdrawal latencies for less than 4 h. Food intake was reduced after all 3 dosages, and fecal output decreased in the 1- and 2-mg/kg groups. The decreases in these parameters were dose-dependent, with the greatest reduction measured over the first 24 h. Our current results indicate that hydromorphone at 2 mg/kg SC is an effective, short-acting analgesic drug in chinchillas that transiently reduces food intake and fecal output. Further studies are needed to evaluate the safety of hydromorphone in animals undergoing surgical procedures and general anesthesia and to determine whether lower doses provide analgesia in different nociceptive models.

Chinchillas (*Chinchilla lanigera*) are a popular animal model, particularly for otologic research. In addition, this species is increasingly maintained as companion animals and therefore frequently presented for veterinary care.[12,27] Chinchillas require effective analgesic protocols for a variety indications, including experimental, elective, and therapeutic surgeries, as well as dental disease and trauma.[21,22] Safe and effective pain management is critical in all species, but particularly in small mammals with high metabolic rates and low stress thresholds, to support a rapid return to normal behavior and food intake. The paucity of research studies in the area of pain management in chinchillas complicate the selection of an optimal analgesic drug, dose, and frequency of administration. Consequently, many chinchillas that need analgesia may be treated with ineffective drugs, receive insufficient doses, or undergo repeated dosing at incorrect intervals, thus leading either to insufficient analgesia or possible adverse effects due to excessively frequent administration.

Little information is available regarding the efficacy and safety of opioids in chinchillas,[13] but more is known about opioid analgesics in guinea pigs.[17,20,24] Hydromorphone is a semisynthetic opiate related to morphine that has primarily μ-opioid receptor agonist activity.[18] Hydromorphone is considered 5 times more potent than morphine, and reported onset times in mammals are within 15 to 30 min, depending on the route of administration.[18] Dosages recommended in dogs and cats for perioperative to severe pain are 0.1 to 0.3 mg/kg every 2 to 6 h.[18] Dosage recommendations for hydromorphone in small mammals, such as rabbits, range from 0.2 to 0.5 mg/kg every 6 to 8 h.[16] In rats, the ED_{50} is 0.16–0.51 mg/kg.[1] Because no studies investigating the efficacy or safety of hydromorphone or morphine in chinchillas have been published previously, doses currently used in chinchillas are likely extrapolated from other species or based on personal clinical experience and anecdotal reports, without evidence for analgesic efficacy.

Opioids can cause gastrointestinal hypomotility in rodents, potentially leading to gastrointestinal stasis and constipation.[14,16,22,26] Chinchillas and other hindgut-fermenting small mammals (for example, guinea pigs, rabbits) are prone to developing gastrointestinal stasis; therefore, gastrointestinal adverse effects secondary to administration of hydromorphone and other opioid analgesics are of particular concern. Other adverse effects of hydromorphone administration include sedation, respiratory depression, and nausea.[14,16]

The objective of the current study was to evaluate analgesic efficacy of subcutaneous hydromorphone in chinchillas by measuring hindlimb withdrawal latencies after exposure to a thermal noxious stimulus and to assess potential effects on food intake and fecal output. We hypothesized that subcutaneous administration of hydromorphone would prove effective in providing thermal antinociception and that a dose-dependent decrease in food intake and fecal output would occur at high doses.

Materials and Methods

This study was approved by the University of Wisconsin–Madison, School of Veterinary Medicine IACUC. Adult chinchillas (n = 16; 11 male, 5 female; age, 1 to 2 y; weight, 0.61 ± 0.1 kg (range, 0.44 to 0.86 kg) were obtained from a commercial breeder (R and R Chinchillas, Jenera, OH)). Animals were housed in a climate-controlled room with a 12:12-h light cycle. Room temperature was maintained at 21 to 23 °C. The chinchillas were housed in individual cages (0.69 m × 0.69 m × 0.46 m; 6-cage Rabbit Housing Unit, Allentown Caging, Allentown, NJ) with perforated plastic excreta pans. Each cage contained a plastic hide box, as well as cardboard tubes and a piece of natural wood for foraging. At least once weekly, chinchillas had an opportunity to exercise and socialize in a playpen (1.8 m × 0.9 m), which contained a dust bath. The chinchillas were fed a commercial pelleted rabbit diet (MannaPro Rabbit pellets,

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MannaPro Products, Chesterfield, MO) and received tap water from a rabbit ball-tipped water bottle without restriction. Food was offered in a ceramic food bowl on the cage floor. The location of the water bottle and food bowls were the same throughout acclimatization and the study period. Food and water were always available to the animals.

All chinchillas were acclimated to the housing conditions for at least 2 wk prior to starting the experiments. All animals were deemed to be clinically healthy according to repeated physical examination, daily visual examinations, and monitoring of food intake and fecal output throughout the study. No complications, such as foot lesions, or other health issues occurred throughout the course of the study.

Analgesimetry experiments were performed by using a plantar testing device (Plantar Test with Heated Base, ITTC Life Science, Woodland Hills, CA), designed based on the Hargreaves method.[6] The heated glass base's temperature was set at 29 °C, and the radiant heat beam intensity was set at 50%. We measured hindlimb withdrawal latencies (in seconds) in response to a noxious infrared radiant heat stimulus applied to the plantar surface of a hindpaw. The cut-off time was set at 25 s, to avoid tissue damage. Prior to starting the analgesimetry experiment, the chinchillas were acclimated to the Hargreaves apparatus for 15 min daily for 2 wk. For an additional 2 wk, baseline hindlimb withdrawal latency measurements were recorded, twice per foot, as many as 3 times daily. On each experimental day, the chinchillas were placed in the Hargreaves apparatus and allowed to acclimate for 15 min prior to starting measurements. During the acclimation period, both hindlimbs were tested. For the final experiments, the foot that provided more consistent baseline withdrawal latency measurements in each animal was used throughout this study. Measurements were taken 5 min apart at each time point. Two hindlimb withdrawal latencies were recorded at each time point and averaged. When these 2 latencies varied by more than 20%, a third measurement was recorded, and the average of all 3 latencies was used for data analysis.

In a randomized (www.randomizer.org), blind, controlled, complete crossover design, hydromorphone (2 mg/mL, West-Ward Pharmaceuticals, Eatontown, NJ) was administered at 0.5, 1, and 2 mg/kg SC. Saline was administered at 0.5 mL/kg SC in the control group. Due to the nature of a complete crossover design, all animals were assigned to all treatment and control group in a randomized fashion. The observer was blind to treatment group. Hindlimb withdrawal latencies were measured at 0 (baseline), 1, 2, 4, and 8 h after drug administration. Body weight, as well as daily food intake and fecal output (in grams per kilogram body weight), were measured the day prior to starting each treatment (baseline) and for 6 d after drug administration. The washout period between treatments was at least 7 d.[8,15] Animals were monitored for adverse effects, including neurologic deficits and signs of sedation after drug administration.

Statistical analysis. Commercial software (SigmaPlot 13, Systat Software, San Jose, CA) was used to perform the data analysis. The data were evaluated for normal distribution by using the Shapiro–Wilk test and for equal variance by using the Brown–Forsythe test. The data were transformed, when necessary. The data were analyzed for effects of drug and time by using a repeated measures 2-way ANOVA, with the Holm–Sidak method used for posthoc analysis. A P value less than 0.05 was considered statistically significant.

Results

Hydromorphone at 2 mg/kg resulted in a significant increase in withdrawal latencies at 1 h compared with baseline (P = 0.01) and at 2 h compared with the control group and baseline latencies (P = 0.002 and P = 0.008; Figure 1). At 4 and 8 h, no differences in withdrawal latencies were found at the 2 mg/kg dose. At 0.5 mg/kg, a statistical trend toward an increase in latency was present at the 2-h time point compared with the control (P = 0.078).

Food intake on day 1 after drug administration was significantly reduced, compared to the control group, in a dose-dependent manner for all evaluated dosages of hydromorphone (0.5 mg/kg, 0.3% ± 14.9%; 1 mg/kg, 11.3% ± 23.1%; 2 mg/kg, 17.3% ± 37.3%); variance, Figure 2). In the 1- and 2-mg/kg groups, food intake increased again by day 2 but remained significantly ($P < 0.05$) lower than for the control group. By day 3, hydromorphone groups showed no significant differences in food intake compared with the control group.

For the first 2 d, fecal output was reduced in the 1- and 2-mg/kg hydromorphone groups compared with the control group. The greatest decrease fecal output occurred over the first 24 h after drug administration (0.5 mg/kg, 7.8% ± 12.8%; 1 mg/kg, 17.7% ± 23.7%; 2 mg/kg, 24.3% ± 32.8%; control group, 2.9% ± 12.6%). Fecal output remained significantly ($P < 0.05$) reduced in the 2-mg/kg group compared with baseline levels for 6 d after drug administration (Figure 3). Hydromorphone at the 0.5-mg/kg dose did not significantly change fecal output.

Body weight did not change significantly after hydromorphone administration. No sedation or other adverse effects were observed in chinchillas after the administration of hydromorphone at 0.5 to 2 mg/kg SC.

Discussion

Hydromorphone administered subcutaneously in chinchillas at 0.5 and 1 mg/kg failed to induce analgesia in the thermal nociception model used in this study, whereas at 2 mg/kg analgesia was induced for less than 4 h. The ED_{50} for subcutaneously administered hydromorphone in rats in high-intensity thermal nociception models has been reported as 0.28 (0.16–0.51) mg/kg.[1] In mice, the ED_{50} of subcutaneous hydromorphone in a thermal nociception model was 0.2–0.24 mg/kg.[9] These doses are substantially lower than the effective analgesic dose of hydromorphone in chinchillas in our study. However, in guinea pigs, which are more closely related to chinchillas than rats and mice, the effective analgesic dose of morphine has been reported to be higher. In guinea pigs, morphine at 10 mg/kg SC in thermal nociception models, at 6 to 12 mg/kg SC (ED_{50} 6.3 mg/kg) in mechanical nociception model, and 5 mg/kg SC in an electrical stimulation model, have been reported to provide analgesia.[4,5,15] Given that hydromorphone is considered 5 times more potent than morphine, the 2-mg/kg dose of hydromorphone that provided analgesia to chinchillas in our study seems comparable to the effective morphine dosages reported in the literature for guinea pigs.[4,15] Although thermal nociception models are accepted methods to evaluate analgesic efficacy in animals, they may overestimate drug dose requirements to provide analgesia for other types of pain stimuli (for example, surgical pain).[19] Therefore, hydromorphone at doses lower than 2 mg/kg might achieve quantifiable analgesia in nonthermal nociception models, such as postsurgical models, in chinchillas.

The duration of analgesic effects of hydromorphone in chinchillas after subcutaneous administration at 2 mg/kg was less than 4 h, which is consistent with dosing recommendations in other species. Buprenorphine has been suggested to be long-acting in chinchillas, and dosing intervals of 6 to 12 h have been reported anecdotally.[22] However, recent research in chinchillas has shown that buprenorphine at 0.2 mg/kg re-

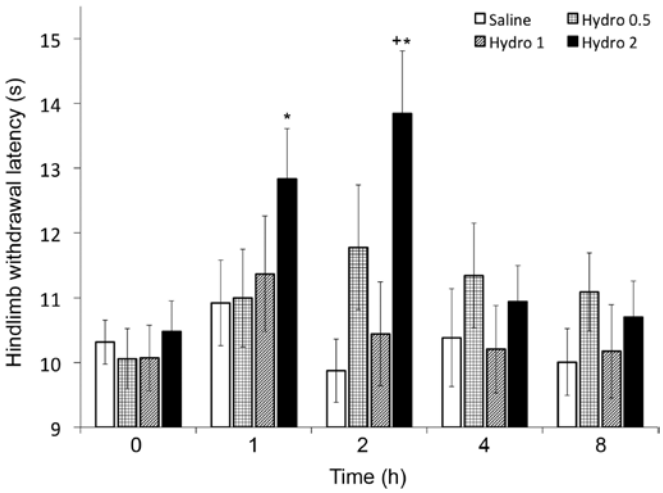

Figure 1. Hindlimb withdrawal latencies (s, mean ± SEM) in response to a thermal noxious stimulus in 16 chinchillas after the administration of a single dose of hydromorphone at 0.5, 1, and 2 mg/kg SC (Hydro 0.5, Hydro 1, and Hydro 2, respectively) in a randomized, blind, controlled, complete crossover design. In all experiments, controls received saline subcutaneously. +, Significant ($P < 0.05$) difference compared with control group at the same time point; *, significant ($P < 0.05$) difference compared with baseline value within the same group.

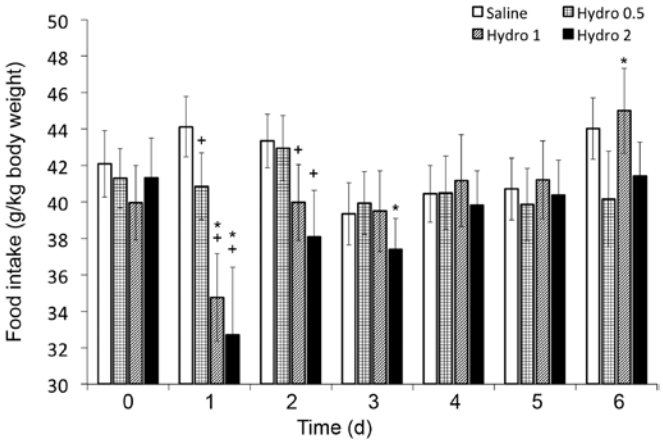

Figure 2. Food intake (g/kg body weight, mean ± SEM) in 16 chinchillas after the administration of a single dose of hydromorphone at 0.5, 1, and 2 mg/kg SC (Hydro 0.5, Hydro 1, and Hydro 2, respectively) in a randomized, blind, controlled complete crossover design. In all experiments, controls received saline subcutaneously. +, Significant ($P < 0.05$) difference compared with control group at the same time point; *, significant ($P < 0.05$) difference compared with baseline value within the same group.

sulted in increased limb withdrawal latency for less than 4 h.[13] Various sustained-release formulations of buprenorphine and hydromorphone have shown prolonged analgesic effects in rats, and therefore future research should focus on the evaluation of these formulations in chinchillas, to avoid the frequent handling needed for the administration of opioid analgesics, which might have detrimental effects on the animals.[3,8,23,25]

The time to peak analgesic effects of subcutaneous hydromorphone in mice has been estimated as 45 min after injection.[9] In our study, withdrawal latencies increased within 1 h but peaked at 2 h after administration. Difference between species or the methodology used in these 2 studies may be responsible for the difference in peak analgesic effect time.

The negative effects of opioids on gastrointestinal motility and transit time, leading to opiate-induced constipation have

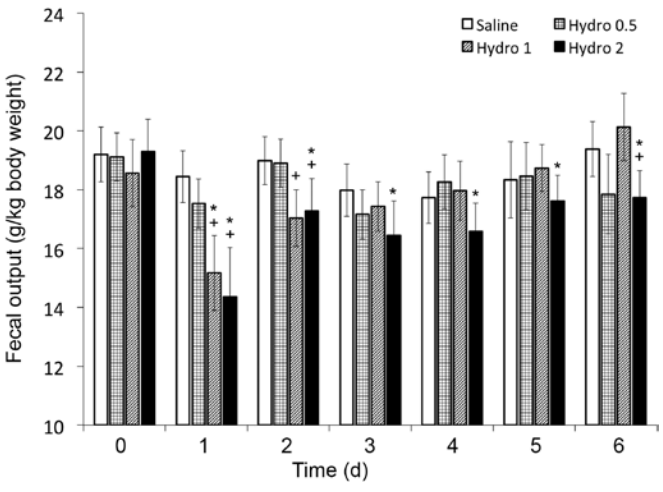

Figure 3. Fecal output (g/kg body weight, mean ± SEM) in 16 chinchillas after the administration of a single dose of hydromorphone at 0.5, 1, and 2 mg/kg SC (Hydro 0.5, Hydro 1, and Hydro 2, respectively) in a randomized, blind, controlled, complete crossover design. In all experiments, controls received saline subcutaneously. +, Significant ($P < 0.05$) difference compared with control group at the same time point; *, significant ($P < 0.05$) difference compared with baseline value within the same group.

been well documented in rodents and other species.[2,7,10,14] Inhibition of gastric emptying, increased pyloric muscle tone, and blockade of peristalsis, among other mechanisms, are responsible for the delayed gastrointestinal transit time and risk of development of constipation.[7] Constipation is a common problem in chinchillas, and therefore negative effects of administered opioids are a concern in this species.[11] Decreases in food intake and fecal output also occurred in hydromorphone-treated chinchillas in the current study. High doses of buprenorphine have been reported to reduce food intake and fecal output in chinchillas.[13] At the determined analgesic dose of buprenorphine at 0.2 mg/kg, chinchillas undergoing thermal analgesimetry experiments had an average reduction in food intake of 24.9% ± 15.9%.[13] This reduced food intake over the first 24 h after drug administration is comparable to the 17.3% ± 37.3% reduction after administration of hydromorphone at 2 mg/kg SC in our current study. Furthermore, the reduction in fecal output over the same period is also comparable between the buprenorphine (0.2 mg/kg SC, 29.2% ± 17.5%) and the hydromorphone-treated chinchillas (2 mg/kg, 24.3% ± 32.8%).[13] In both studies, the reductions in food intake and fecal output were self-limiting and did not have clinical consequences. However, because we evaluated healthy chinchillas only, it cannot be ruled out that hydromorphone administered to a systemically diseased chinchilla or to chinchillas undergoing general anesthesia and surgical procedures might show more pronounced effects on food intake or fecal output than reported in this study.

In rats given hydromorphone at 4 mg/kg SC, transient excitatory effects, including exophthalmos and muscle rigidity within 30 min after drug administration, have been reported.[25] In guinea pigs, morphine at 10 mg/kg IP led to signs of sedation, which lasted about 60 min.[17] In our current study, chinchillas administered hydromorphone at 0.5 to 2 mg/kg SC showed no opioid-related excitatory effects.

Limitations of this study include the use of a single nociception model only and the evaluation of adverse effects only in healthy chinchillas. Further studies are needed to evaluate the safety of hydromorphone in animals undergoing surgical

procedures and general anesthesia and to determine whether lower doses provide analgesia in different nociceptive models.

In conclusion, the results of this study indicate that hydromorphone at 2 mg/kg SC is an effective, short-acting analgesic drug in chinchillas that transiently decreases food intake and fecal output.

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