Subcutaneous hydromorphone hydrochloride provides antinociception with transient adverse effects in four-toed hedgehogs (*Atelerix albiventris*)

Macy L. Peterson, BS; Christoph Mans, Dr med vet, DACZM; Grayson A. Doss, DVM, DACZM*

Department of Surgical Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI

*Corresponding author: Dr. Doss (gdoss@wisc.edu)

OBJECTIVE
To evaluate the efficacy and safety of hydromorphone administered SC in four-toed hedgehogs (*Atelerix albiventris*).

ANIMALS
12 healthy adult hedgehogs.

METHODS
Hedgehogs underwent 2 randomized, blinded, placebo-controlled, complete crossover studies. Hind limb withdrawal latencies in response to an acute thermal noxious stimulus were measured to evaluate the antinociceptive efficacy of hydromorphone. Baseline latencies were obtained prior to injection and collected again at 0.5, 1, 2, 4, and 6 hours following injection. Based on pilot studies, single doses of SC hydromorphone at 0.15 and 0.3 mg/kg were evaluated for efficacy in crossover trials. Safety of single (0.15 and 0.3 mg/kg) and multiple doses of hydromorphone (0.3 mg/kg, SC, q 4 h, for 3 doses) was also assessed. In addition to monitoring behavior during latency measurements, animals were evaluated for overt sedation and daily changes in food intake, body weight, and running wheel activity for 6 days after injection to evaluate for adverse effects.

RESULTS
Hydromorphone at 0.15 mg/kg provided antinociception lasting < 4 hours, and 0.3 mg/kg provided antinociception lasting < 6 hours. Hydromorphone produced transient abnormal behaviors at both doses, including vocalization, chewing motions of the jaw, and paw raising. There were no statistically significant differences in body weight or running wheel activity between treatments for single or multiple doses of hydromorphone. Three doses of 0.3 mg/kg hydromorphone (q 4 h) produced a statistically significant decrease (median, −9.7%; range, −64% to 10%) in 6-day total food intake.

CLINICAL RELEVANCE
Subcutaneous hydromorphone (0.15 to 0.3 mg/kg) can be used for short-term antinociception with transient adverse effects in hedgehogs.

Keywords: hydromorphone, antinociception, hedgehog, analgesia, dysphoria

The distinctive anatomy and defensive behavior of hedgehogs make administering oral medications challenging, and injectable analgesic options are therefore more suitable for hedgehogs. Hedgehogs frequently curl into a tight ball when stimulated or stressed, completely hiding their head, limbs, and ventrum. The SC route is more practical in awake hedgehogs and avoids the need to administer large injection volumes in their relatively small-muscle bellies. Additionally, a recent study demonstrated that a single injection of buprenorphine hydrochloride has a greatly prolonged duration of action when administered SC into the mantle of hedgehogs.

Hydromorphone is a semisynthetic, moderately lipophilic opioid that exerts its primary analgesic effects through µ-receptor activity. This drug has a similar adverse effect profile to morphine at equianalgesic doses.

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and is widely used in veterinary medicine to treat moderate to severe pain.\textsuperscript{3,4} Despite the wide availability of hydromorphone in veterinary practice, its efficacy and safety in hedgehogs are currently unknown.

The goals of this study were to evaluate the efficacy and safety of SC hydromorphone hydrochloride in four-toed hedgehogs. We hypothesized that SC hydromorphone would provide antinociception lasting for several hours with minimal sedative effects in hedgehogs. We also hypothesized that hydromorphone would have a longer duration of action in hedgehogs when administered SC compared to its duration in other species.

**Methods**

This study was approved by the University of Wisconsin-Madison School of Veterinary Medicine IACUC (protocol V005874). Twelve captive-bred four-toed hedgehogs (9 males, 3 females) approximately 8 months old with a mean ± SD weight of 470 ± 113 g were obtained from a commercial breeder. Animals were kept individually in ventilated plastic enclosures (84 X 51 X 36 cm) within a climate-controlled room maintained at 27 °C with a 12:12 hours light cycle. Each enclosure was lined with a thin cardboard sheet and contained a running wheel and a hide box filled with shredded paper for burrowing. Hedgehogs were maintained on a commercial low-fat cat kibble (Adult Weight Management Chicken & Rice Formula; Purina Pro Plan) and provided a bowl of water ad libitum. All hedgehogs were acclimated to the housing conditions for several weeks before the start of pilot trials. They were deemed healthy based on serial physical examinations and long-term monitoring of body weight, food intake, and activity level. Trials occurred in a separate climate-controlled room maintained within 3 °C (5 °F) of the housing room.

Hydromorphone (2 mg/mL; West-Ward) or an equivalent volume of sterile saline (0.9% NaCl) solution was administered SC at a depth of 1.3 cm with an insulin syringe (U-100 insulin syringe [29 gauge, 0.3 mL]; UltiCare VetRx) in the area of dorsal spined skin (mantle) over the right scapula while the awake hedgehog was rolled into a defensive ball. This specific depth and location of injection were chosen to target intra-adipose deposition of the drug.

Analgesimetry was performed with a Hargreaves apparatus (Plantar Analgesia Meter; ITTC Life Science) as previously described for this species.\textsuperscript{2,3} Briefly, hedgehogs were placed in ventilated, opaque measurement chambers (22 X 17 X 13.5 cm) on a heated glass surface maintained at 29 °C. A noxious, infrared radiant heat stimulus (set to 50% maximum intensity) was applied focally to a metatarsal pad, and the thermal stimulus was immediately removed once the hedgehog moved the targeted limb. If no limb withdrawal response occurred, the thermal stimulus was terminated after 20 seconds to prevent tissue damage. The latency of limb withdrawal was recorded in seconds. The same metatarsal pad was used for all treatments and was examined for gross abnormalities before each measurement. If the hedgehog rolled up into a defensive posture, preventing access to the metatarsal pad for thermal stimulus application, the hedgehog was gently removed from the chamber and then replaced to encourage unrolling. Hedgehogs were allowed to acclimate for a minimum of 1 minute after being replaced into the chamber before the thermal latency measurement was reattempted. Thermal withdrawal latency measurements for baseline measurements and for each time point following the injection were performed in duplicate 5 minutes apart. If the 2 measurements varied by more than 20%, a third measurement was performed, and the 3 latencies were averaged to obtain the latency for that time point. Hedgehogs were placed into the Hargreaves chamber at least 5 minutes prior to each measurement to promote unrolling and access to the metatarsal pad and were removed from the chamber immediately after the second or third measurement was completed. A single observer (MLP) who was blinded to treatment performed all antinociceptive measurements. All hedgehogs were acclimated to the Hargreaves apparatus for several weeks prior to study onset.

Using a previous scoring system,\textsuperscript{2} hedgehogs were assessed for evidence of sedation when handled for each thermal latency measurement, including a baseline level prior to injection. A single observer (MLP) blinded to treatment performed all sedation scoring. Changes in food intake, running wheel activity, and body weight were assessed daily and compared to baseline values to assess safety. Baseline values for food intake, running wheel activity, and body weight were collected by calculating an average of daily measurements collected over the 3 days immediately prior to injection. For running wheel activity, bicycle odometers (Model DCY-16; Dream Sport) were attached to commercial running wheels designed for four-toed hedgehogs (Carolina Storm Wheels) and calibrated using the circumference of the running wheel per the manufacturer’s instructions. The distance traveled in miles was recorded for each 24-hour period. A single observer (MLP) blinded to treatment performed all daily food intake, running wheel activity, and body weight measurements, which were collected in the morning.

**Experimental design**

The study comprised 2 distinct trials to evaluate the antinociceptive efficacy and safety of SC hydromorphone. Three of the hedgehogs failed to acclimate to the Hargreaves apparatus chambers and were therefore not included in the latency trials to avoid inaccurate latency measurements. Seven-day minimum washout periods were utilized between all trials, including pilot trials and the 2 final trials.

**Dose-finding pilot trials**—Hydromorphone was initially evaluated in 9 hedgehogs with a starting dose of 0.1 mg/kg, based on dosing recommendations for ferrets, dogs, and cats.\textsuperscript{4,6,7} Each hydromorphone dose was evaluated in a minimum of 2 or 3 hedgehogs, and dose escalation was performed to find efficacious doses based on thermal latency measurements and...
produced minimal adverse effects. Pilot trials identified that hydromorphone at approximately 0.15 to 1 mg/kg produced measurable thermal antinociception. A high incidence of adverse effects, including excessive vocalization, hyperactivity, ataxia, and vomiting, were noted with the higher doses of 0.5 and 1 mg/kg. Based on the pilot data, hydromorphone doses of 0.15 to 0.3 mg/kg were considered optimal for further evaluation.

Crossover antinociceptive efficacy study—Nine hedgehogs (7 male, 2 female) were administered a single SC injection of 0.15 mg/kg hydromorphone, 0.3 mg/kg hydromorphone, or sterile saline at a dose of 0.3 mL/kg (equivalent volume to 0.3-mg/kg hydromorphone dose) in a randomized, blinded, placebo-controlled, complete crossover study. A hydromorphone concentration of 2 mg/mL was used, and there was a minimum 7-day washout period between treatments. Baseline thermal withdrawal latencies and sedation scores were obtained prior to injection and collected again at 0.5, 1, 2, 4, and 6 hours following injection. Hedgehogs were housed in plastic laboratory rodent enclosures, where they were monitored between latency measurements for the development of adverse behavioral effects. Food intake, body weight, and wheel running data were collected for 6 days following injection.

Multidose adverse effect study—The safety of multiple SC doses of hydromorphone was assessed in a randomized, blinded, placebo-controlled, complete crossover study in 12 hedgehogs (9 male, 3 female). Hedgehogs were administered 0.3 mg/kg hydromorphone SC (q 4 h for 3 doses) or an equivalent volume (0.3 mL/kg) of sterile saline SC (q 4 h for 3 doses). The dosing frequency was chosen based on data obtained in the dose-effect portion of the study. A single observer (MLP) blinded to treatment performed all sedation scoring and monitoring of hedgehogs during the trials for development of adverse behavioral effects. Following a short period of handling for the injections, hedgehogs were placed back into their normal housing for observation. Food intake, running wheel activity, and body weight data were collected in the morning for 6 days following injection. Multidose adverse effect study—The safety of multiple SC doses of hydromorphone was assessed in a randomized, blinded, placebo-controlled, complete crossover study in 12 hedgehogs (9 male, 3 female). Hedgehogs were administered 0.3 mg/kg hydromorphone SC (q 4 h for 3 doses) or an equivalent volume (0.3 mL/kg) of sterile saline SC (q 4 h for 3 doses). The dosing frequency was chosen based on data obtained in the dose-effect portion of the study. A single observer (MLP) blinded to treatment performed all sedation scoring and monitoring of hedgehogs during the trials for development of adverse behavioral effects. Following a short period of handling for the injections, hedgehogs were placed back into their normal housing for observation. Food intake, running wheel activity, and body weight data were collected in the morning for 6 days following the trial day when the injections were administered.

Statistical analysis
Treatment order was randomized for each experimental trial using free online software (Research Randomizer, version 4.0; Geoffrey C. Urbania and Scott Plous), and treatments were balanced between trials days. Commercial statistical software (SigmaPlot, version 13; Systat Software) was used for all data analysis. Normal distribution was evaluated with the Shapiro-Wilk test and the Brown-Forsythe test used for testing the equality of group variances. Data were transformed, if necessary. The data were analyzed for effects of treatment and time with repeated-measures ANOVA, and the Holm-Sidak method was utilized for post hoc analyses. A paired t test and Wilcoxon signed rank test were used to compare 6-day total food intake and 6-day total running wheel activity between multidose treatments, respectively. Values of P < .05 were considered statistically significant. Data are reported as median (range) unless otherwise indicated.

Results

Antinociceptive efficacy study
Hydromorphone at 0.15 mg/kg produced a statistically significant (P ≤ .004) increase in thermal withdrawal latency measurements at the 0.5-hour, 1-hour, and 2-hour time points compared to the control treatment (Figure 1).

Figure 1—Mean ± SEM change in pelvic limb thermal withdrawal latency in seconds for 9 four-toed hedgehogs administered hydromorphone SC at a dose of 0.15 mg/kg (H 0.15 mg/kg), hydromorphone SC at a dose of 0.3 mg/kg (H 0.3 mg/kg), or saline (0.9% NaCl) SC at a dose of 0.3 mL/kg (Control) in a randomized, blinded, placebo-controlled, complete crossover experiment. *Significantly (P ≤ .011) different from the control treatment value at the same time point.

Hydromorphone at 0.3 mg/kg produced a statistically significant (P ≤ .011) increase in thermal withdrawal latency measurements at the 0.5-hour, 1-hour, and 4-hour time points compared to the control treatment. There were no statistically significant (P > .07) differences between hydromorphone treatments at any time point. Hydromorphone at 0.3 mg/kg produced longer-lasting antinociception than hydromorphone at 0.15 mg/kg, but there were no observable differences in magnitude of antinociceptive effect between doses.

There were no statistically significant differences in food intake (Figure 2), body weight, or running wheel activity between treatments (Table 1). Compared to control (mean ± SD, 2 ± 22%), food intake was decreased for hedgehogs administered both 0.15 mg/kg (–15 ± 11%) and 0.3 mg/kg (–17 ± 20%) hydromorphone over the first 24 hours following administration. This change was not statistically significant (P ≥ .078). There were no statistically significant differences in body weight between treatments, and there was no statistically significant increase in running wheel activity during the 24 hours after opioid administration. The sedation score was 0 for all time points for all animals, regardless of treatment.
Multidose adverse effect study

There were no statistically significant differences in body weight or wheel running activity between treatments administered 3 doses of 0.3 mg/kg of hydromorphone. In the first 24 hours after administration (the 24-hour period starting the morning of the multidose trial day and ending the following morning), repeated dosing of hydromorphone resulted in a statistically significant reduction of food intake of –23% (–91% to 13%; \( P = .005 \)) from baseline compared to the change from baseline for the control treatment (3.4%; range, –22% to 67%; Figure 2). Total food intake over the 6-day observation period was significantly lowered by –9.7% (range, –64% to 10%; \( P = .034 \)) following repeated hydromorphone administration (109 g/kg; range, 81 to 219 g/kg) compared to the control treatment (124 g/kg; range, 94 to 313 g/kg). The sedation score was 0 for all time points for all animals, regardless of treatment. There were no statistically significant differences in body weight or running wheel activity between treatments. There was no statistically significant increase in running wheel activity during the 24 hours after opioid administration.

Observed behavioral effects in both studies

Abnormal behaviors noted were vocalization, chewing-like motions of the mandible, paw raising, licking, and hyperactivity (Supplementary Videos S1 and S2). Vomiting was noted in a single hedgehog following single injections of both doses and multiple doses of hydromorphone. The observed adverse effects did not last longer than 3 hours following hydromorphone injection in all hedgehogs.

Adverse effects

Antinociceptive efficacy study—Adverse effects were observed in hedgehogs administered hydromorphone, with a higher occurrence of adverse effects at the higher hydromorphone dose evaluated (Supplementary Table S1). Adverse effects were noted in 8 of 9 hedgehogs administered 0.15 mg/kg of hydromorphone, in 9 of 9 hedgehogs administered 0.3 mg/kg of hydromorphone, and in 7 of 9 hedgehogs following saline administration. Two hedgehogs exhibited behavior where they rubbed the side of their body against adjacent structures following both saline and 0.3 mg/kg of hydromorphone injections. A single animal both displayed orbital tightening and laid in a sternal position for extended periods following single injections of 0.15 and 0.3 mg/kg of hydromorphone.

Table 1—Various safety parameters following subcutaneous injections of hydromorphone compared to saline control in four-toed hedgehogs. Values are reported as median (range). Single injections were administered as 0.15 or 0.3 mg/kg (dose effect) or as multiple injections (multidose safety) at 0.3 mg/kg (3 total doses, 4 hours apart).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Hydromorphone (0.15 mg/kg)</th>
<th>Hydromorphone (0.3 mg/kg)</th>
<th>Multidose adverse effect study (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-day total food intake (g/kg of body weight)</td>
<td>148 (103 to 196)</td>
<td>134 (89 to 189)</td>
<td>131 (77 to 186)</td>
<td>124 (94 to 313)</td>
</tr>
<tr>
<td>Percentile change in total 6-day food intake from control (%)</td>
<td>–13 (-19 to 19)</td>
<td>–6 (-36 to 28)</td>
<td>–10 (-64 to 10)</td>
<td>–10 (-64 to 10)</td>
</tr>
<tr>
<td>Percentile change in body weight on day 6 compared to baseline (%)</td>
<td>2 (1 to 7)</td>
<td>3 (-1 to 7)</td>
<td>1 (-2 to 2)</td>
<td></td>
</tr>
<tr>
<td>Running wheel activity during 24 h posttreatment (day 1; miles)</td>
<td>0.02 (0 to 4.1)</td>
<td>0.12 (0 to 4.2)</td>
<td>0.06 (0 to 2)</td>
<td>0.2 (0 to 6.3)</td>
</tr>
</tbody>
</table>

*There is a statistically significant difference (\( P < .05 \)) between treatments.
Multidose adverse effect study—Adverse effects were noted in 9 of 12 hedgehogs administered 3 doses of hydromorphone compared to 0 of 12 hedgehogs administered 3 doses of saline. Three hedgehogs (3/12) that received 0.3 mg/kg of hydromorphone for 3 doses began using their running wheels within 30 minutes of being placed back in their home enclosure. This behavior was not observed following the control treatment. Hedgehogs were returned to their enclosures immediately after injections in the multidose trial to minimize any effect of handling on food intake or running wheel activity. Once returned, hedgehogs often retreated out of view into their hide box.

Discussion

The duration of antinociception following SC hydromorphone in hedgehogs was dose dependent in this study. A dose-dependent effect has also been reported with SC methadone and buprenorphine in hedgehogs. The duration of the effect of 0.15 mg/kg of hydromorphone in hedgehogs (< 4 hours) is shorter than for a slightly higher dose (0.2 mg/kg, SC) in ferrets (4 hours) and comparable to 0.1 mg/kg of hydromorphone SC in cats (3.5 hours). The duration of effect for the higher 0.3-mg/kg hydromorphone dose in hedgehogs (< 6 hours) is comparable to cats (< 6 hours) administered IM hydromorphone. Direct comparisons to studies in other species are challenging due to differences in doses evaluated and analgesimetry methodology. The duration of effect of hydromorphone is noticeably longer than that of methadone (< 2 hours) in hedgehogs. Conversely, the antinociceptive response following SC buprenorphine hydrochloride (0.01, 0.03, and 0.05 mg/kg) in hedgehogs is markedly longer than hydromorphone, lasting up to 36 to 48 hours. Given the similarities in study design, these disparities in antinociceptive duration are likely attributable to differences in the individual opioid properties (eg, lipophilicity, receptor binding affinity). There is abundant adipose tissue and limited vascularity beneath the spiny mantle of four-toed hedgehogs, and deep SC injections in this area are likely to result in intra-adipose deposition of the drug, influencing both pharmacokinetics and pharmacodynamics. Hydromorphone is less lipophilic than both methadone and buprenorphine but has a high receptor affinity similar to buprenorphine.

Similar to methadone but in contrast to buprenorphine, hydromorphone’s magnitude of antinociceptive effect was not dose dependent in hedgehogs in this study. The cause of these differences remains unclear but likely involve differences in the properties of the different opioids. While higher doses of hydromorphone may have increased the magnitude or duration of the antinociceptive effect in hedgehogs, higher doses were not further evaluated due to the increased incidence of adverse effects with higher doses in the pilot trials.

Multiple doses of SC hydromorphone resulted in a statistically significant decrease in food intake. One potential explanation is that food intake was reduced secondary to the drug-induced adverse effects. The higher incidence rate of adverse effects with 0.3 mg/kg of hydromorphone, combined with the administration of multiple injections at this dose, may have led to a significant decrease in food intake with this treatment. Additionally, single doses of 0.15 and 0.3 0.15 and 0.3 mg/kg of hydromorphone produced a mean decrease in food intake of ~15% and ~17% compared to baseline levels, respectively. While not statistically significant, this change in food intake could become clinically relevant, particularly when analgesia is provided to debilitated hedgehogs.

Hydromorphone produced adverse effects at both 0.15 and 0.3 mg/kg in this study. Some hedgehogs in the single-dose control group also displayed adverse effects (Supplementary Table S1). It is possible that some of these behaviors, like chewing motions of the mandible, paw raising, and periods of hyperactivity, are normal in four-toed hedgehogs but are displayed at a higher frequency or intensity following hydromorphone administration or even saline injection. The high frequency of vocalization in the hedgehogs may reflect a dysphoric-like state, which is common with opioid administration, including hydromorphone, in multiple species. Additionally, dysphoria and excitation, including vocalization, are more commonly encountered when opioids are administered at higher doses. Hydromorphone at 0.1 mg/kg, SC, produced dysphoria with vocalization in cats. Dogs administered 0.1 and 0.5 mg/kg of hydromorphone, SC, exhibited panting, vomiting, and whining within the first 30 minutes following administration. Interestingly, overt adverse effects were not noted with the administration of SC buprenorphine in hedgehogs, and there is an increased frequency of adverse effects with hydromorphone administration compared to SC methadone in hedgehogs. Only 11% and 33% of hedgehogs administered 0.5 mg/kg and 1.0 mg/kg of methadone SC displayed adverse effects, respectively. However, following a higher methadone dose (1.5 mg/kg), a greater number of hedgehogs (67% to 78%) developed adverse effects. For single injections of hydromorphone in our study, adverse effects were noted in 8 of 9 hedgehogs administered 0.15 mg/kg and in 9 of 9 hedgehogs administered 0.3 mg/kg. These differences could be attributed to species-specific responses to different opioid drugs in hedgehogs, the distinct properties of the different opioids themselves, or both. For example, methadone provides a decreased risk of vomiting in cats and dogs compared to other μ-opioid agonists, like hydromorphone and morphine. Methadone also produced an abnormal behavior in hedgehogs where they stood motionless for extended periods of time, an effect not noted with hydromorphone administration or even saline injection. The high frequency of vocalization in the hedgehogs may reflect a dysphoric-like state, which is common with opioid administration, including hydromorphone, in multiple species.

When comparing the incidence rate of adverse effects between the trials utilizing single versus multiple doses of hydromorphone, the animals receiving single doses appear to have a higher rate of occurrence of most adverse effects (Supplementary Table S1). This distinction is likely due to hedgehogs being immediately returned to their enclosures for the multidose safety trial compared to hedgehogs undergoing latency measurements, where hedgehogs spent extended periods under unobstructed observation.
in an arguably more stressful environment (moved between Hargreaves measurement chamber and plastic rodent enclosures). For the multidose safety trial, hedgehogs were returned to their enclosures immediately after injections were complete to minimize any effect of handling on food intake or running wheel activity, but this may have led to missing subtle behavioral changes, as hedgehogs often retreated out of view into a hide box. It is possible that this difference in methodology may have produced an observer effect on the hedgehogs’ behavior, potentially explaining the differences in observed adverse effect frequency between the control groups. For example, a visible observer influenced whether green iguanas (Iguana iguana) displayed a response to nociceptive testing. Observer presence also influenced postoperative pain behaviors in rabbits. It is possible that the presence of a visible observer in the single-dose experiment similarly affected the results of this study.

This study had a number of limitations. One limitation was the use of healthy animals, which may not reflect how debilitated hedgehogs would respond to hydromorphone administration at the doses evaluated. Additionally, the Hargreaves analgesimetry model, while noninvasive, does not directly compare to other nociceptive tests, like surgical models. Future studies are needed to evaluate the safety of hydromorphone in patients to determine whether the doses evaluated in this study provide adequate antinociception across multiple clinical scenarios.

SC hydromorphone produced short- to moderatelasting antinociception in hedgehogs, with no significant effect on body weight, food intake, and wheel running activity following single-dose administration. Multiple doses of hydromorphone within a 12-hour period produced a significant decrease in food intake. Adverse behavioral effects were noted at all doses but were transient relative to the duration of antinociception.

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Disclosures

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Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org.