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Pharmacokinetics of Hydromorphone after Intravenous and Intramuscular Administration in Male Rhesus Macaques (*Macaca mulatta*)

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This study reports the pharmacokinetics of hydromorphone after intravenous and intramuscular administration to rhesus macaques (*Macaca mulatta*). Hydromorphone (0.075 mg/kg) was administered intravenously as a bolus or intramuscularly on separate occasions to healthy, socially housed, socially reared, adult, intact male rhesus macaques (n = 4). Blood samples were collected prior to and until 10 h after administration. Serum hydromorphone concentrations were analyzed with liquid chromatography-mass spectrometry. Compartment models were fit to time–concentration data. A 3-compartment model with input in and elimination from the central compartment best fit intravenous data, whereas a 1-comparment model best fit intramuscular data. After intravenous administration, the median clearance and terminal half-life were 37.7 (range, 33.7 to 47.1) mL/kg/min and 142 (range, 131 to 218) min, respectively. The median (range) elimination half-life after intramuscular administration was 81.5 (77.2 to 92.5) min. Median intramuscular bioavailability was 92% (range, 75% to 104%). Rhesus macaques maintained concentrations greater than or equal to 4.0 ng/mL for at least 2 h after intravenous and intramuscular administration. The disposition of hydromorphone was characterized by a large volume of distribution and moderate clearance. Intramuscular administration resulted in rapid and almost complete drug absorption. Whole-body pruritus, sedation, and decreased appetite were observed in all macaques after initial drug administration.

Hydromorphone is a semisynthetic opioid that provides analgesia through μ-agonist activity. Estimated to be 5 to 10 times more potent than morphine,[5,8,19,25] hydromorphone was first introduced to human medicine in the 1920s and is actively used for the management of chronic pain (for example, cancer-like pain) as well as acute pain in humans.[5,25] Extensive case reports, research studies, and veterinary pharmaceutical formularies support the clinical use of hydromorphone in pain management protocols for traditional small animal veterinary species (for example, dogs and cats);[21,24,27,30,32,33] however, no veterinary literature documents the clinical use of hydromorphone in pain management protocols for nonhuman primates.

Although single-dose pharmacokinetic profiles of intravenous, subcutaneous, and experimental liposome-encapsulated hydromorphone in rhesus macaques have been described,[17] no pharmacokinetics profiles of intramuscular hydromorphone have been described in this species. The purpose of this study was to characterize the disposition of low-dose hydromorphone after intravenous and intramuscular administration in rhesus macaques (*Macaca mulatta*). In this way, we provide bioavailability data to facilitate the assessment of hydromorphone for incorporation into veterinary pain management protocols for nonhuman primates.

Materials and Methods

Animals. Four, healthy, adult, intact male rhesus macaques (*Macaca mulatta*) of Indian origin were used in this study (age, 10 ± 2 y [mean ± 1 SD]; weight, 17± 2 kg; body condition score [maximum, 5], 3.5 [range, 2.5 to 4.0]). Macaques were opioid-naïve and drug-free for at least 2 wk before start of each pharmacokinetic trial. Animals were captive-born, socially reared, and socially housed throughout this study at the AAALAC-accredited California National Primate Research Center and maintained in accordance to recommendations outlined in the *Guide for Care and Use of Laboratory Animals*.[1,2,14,29] Positive-reinforcement training was used to condition macaques to all restraint techniques used in the study including, but not limited to, arm present, target touch, and head present.[4] Macaques were fed a commercial diet (4047 Old World Monkey Chow, Purina Mills, St Louis, MO), and they were provided daily allocations of produce or mixed grains for enrichment. Water was available ad libitum. Animals were maintained on 12:12-h light:dark cycles. All experimental procedures were approved by the IACUC of the University of California, Davis.

Instrumentation and drug administration. On day of experimentation, conscious macaques willingly entered restraint chairs used to facilitate drug administration and time-sensitive phlebotomy. An intravenous bolus of 0.075 mg/kg hydromorphone hydrochloride (Hydromorphone Injection, Hospira, Lake Forest, IL)[12] was administered into the right cephalic vein of each monkey by using a 23-gauge needle attached to a 3-mL syringe. Serial 1-mL blood samples were collected by using 23-gauge needles attached to 3-mL syringes and transferred to 3-mL serum tubes after venipuncture of the left cephalic vein in each monkey. Blood samples were collected prior to hydromorphone administration and at 2, 5, 10, 15, 20, 30, and 60 min and 1.5, 2, 4, 6, 8, and 10 h after administration.

After at least 2 wk of rest, conscious macaques again willingly entered restraint chairs for drug administration and time-sensitive phlebotomy. Intramuscular injections were administered into the right or left quadriceps muscles by using a 23-gauge needle and 3-mL syringe. Serial 1-mL blood samples were

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collected by using 23-gauge needles attached to 3-mL syringes and transferred to 3-mL serum tubes after venipuncture of the left cephalic vein in each monkey. Blood samples were collected prior to hydromorphone administration and at 2, 5, 10, 15, 20, 30, and 60 min and 1.5, 2, 4, 6, 8, and 10 h after administration. In both the intravenous and intramuscular studies, blood samples at 0 to 30 min were collected from macaques after voluntary arm presentation in the restraint chair, whereas those from 60 min to 10 h were collected from macaques after voluntary arm presentation in home cages.

Observation of side-effects. Macaques were continuously visually monitored for side effects from the time of initial drug administration until 2 h after initial administration. Macaques then were visually monitored for side effects during 5 to 10 min focal observations at 4, 6, 8, 10, 24, 48, and 72 h after initial drug administration. Experienced nonhuman primate handlers watched for nonspecific signs of sedation, injection-site pruritus, whole-body pruritus, depression, vomiting, diarrhea, constipation, anorexia or poor appetite, and phlebotomy complications (for example, bruising, hematoma formation, and so forth).

Drug analysis. After sample collection, blood was held at room temperature for more than 20 min to ensure complete clot formation. Serum was separated by centrifugation at 10 °C and 1462 × *g* (Allegra 6R Centrifuge, Beckman Coulter, Brea, CA) and was stored at –70 °C until analysis for hydromorphone concentration. Hydromorphone in macaque serum was quantified by liquid chromatography–mass spectrometry analysis of protein-precipitated samples. The concentration of hydromorphone in each sample was determined according to the internal-standard method (d3-hydromorphone, Toronto Research Chemicals, Ontario, Canada) by using the peak area ratio and linear regression analysis. Quantitative analyses were performed on a triple-quadrupole mass spectrometer (TSQ Quantrum Ultra, Thermo Scientific, San Jose, CA) equipped with a heated electrospray ionization probe. Data was processed by using LCQuan software (version 2.6, Thermo Scientific). The triple-quadrupole mass spectrometer was coupled with a chromatographic system (1100 LC System, Agilent, Santa Clara, CA). Chromatographic separation used an activated charcoal column ($ACEC_{18}$, 100 × 2.1 mm, 3.0-µm; MacMod, Chadds Ford, PA) and a linear gradient of acetonitrile in water with a constant 0.20% formic acid at a flow rate of 0.35 mL/min (Burdick and Jackson, Muskegon, MI). Prior to analysis, the serum proteins, controls, and calibrators were extracted by solid-phase extraction (Polychrom Clin II cartridges, SPEware, Baldwin, CA). The limit of quantitation, that is, the lowest concentration of analyte that could be reliably detected after the incorporation of predefined laboratory standards to minimize bias and imprecision, was 0.10 ng/mL.[3]

Three quality-control samples (0.30, 35, and 160 ng/mL) were used to validate the hydromorphone rhesus macaque serum assay. These quality-control samples were analyzed at least 5 times throughout the study, and the reported mean ± 1 SD were calculated. Accuracy (percentage nominal concentration) was calculated as the ratio between mean measured concentrations of the quality-control samples as compared with the actual concentrations in the quality-control samples. Accuracy was found to be 88%, 89%, and 90% at 0.30, 35, and 160 ng/mL, respectively. Precision (percentage relative SD) was calculated as the ratio of the SD and the mean concentrations. Precision was 13%, 5%, and 3% at 0.30, 35, and 160 ng/mL, respectively. Accuracy greater than 85% and precision less than 15% were deemed acceptable.

Pharmacokinetic analysis. Pharmacokinetic analyses were conducted by using WinNonlin 6.1 (Pharsight, Cary, NC). Nonlinear least-squares regression was conducted on serum hydromorphone time–concentration data. Two- and 3-compartment models with input in and elimination from the central compartment (where appropriate) were fitted to the serum time–concentration data after intravenous hydromorphone administration for each macaque. One- and 2-compartment models with first-order input in and elimination from the central compartment (where appropriate) were fitted to the serum time–concentration data after intramuscular hydromorphone administration for each macaque. Data were weighted by the reciprocal of the predicted concentration squared. The best-fitting model was selected by visual observation of the residual plot and by use of the Akaike Information Criterion.[7,34] The parameters estimated by the model were A, B, C, α, β, γ (intravenous) and the absorption rate constant, apparent volume of distribution, and the K_{10} rate constant (intramuscular). A, B, and C are coefficients and α, β, and γ are exponents in the equation $C_t = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$, where C_t is concentration of hydromorphone at time *t*. Other pharmacokinetic parameters were calculated by using standard pharmacokinetic equations.[6,7] Values for pharmacokinetic parameters are presented as median (range).

Results

Hydromorphone concentrations were higher than the limit of quantitation (0.10 ng/mL) for the duration of the study (10 h) in all monkeys (Figures 1 and 2). A 3-compartment model with bolus input in and first-order elimination from the central compartment best fit the time–concentration data after intravenous administration of 0.075 mg/kg hydromorphone. Pharmacokinetic parameters for the intravenous study are presented in Table 1. A 1-compartment model with first-order input in and first-order elimination best fit the time–concentration data after intramuscular administration of 0.075 mg/kg hydromorphone. Pharmacokinetic parameters for the intramuscular study are presented in Table 2. Median bioavailability after intramuscular administration was 92% (range, 75% to 104%). Hydromorphone concentrations were greater than or equal to 4.0 ng/mL for at least 2 h after intravenous and intramuscular administration. Hydromorphone concentrations were 0.40 ng/mL to 6.0 ng/mL for 2 h after intravenous administration and 4 to 6 h after intramuscular administration.

No significant adverse effects, such as markedly decreased (or increased) respiratory rate, were noted after hydromorphone administration in any of the macaques during either study. After intravenous and intramuscular administration of hydromorphone, macaques appeared to be mildly sedated; however, all were quick to respond to any visual or auditory stimuli during this period (as long as 2 h after drug administration). No injection-site pruritus was noted, but mild to marked whole-body pruritus (for example, scratch or nose wipe) was noted in all animals for as long as 45 min after drug administration. Macaques had decreased appetite for as long as 6 h after drug administration.

Discussion

This study reports the pharmacokinetics of 0.075 mg/kg hydromorphone after intravenous and intramuscular administration in adult, male rhesus macaques (*Macaca mulatta*). As mentioned previously, no published veterinary literature documents clinical use of hydromorphone for pain management in any species of nonhuman primates; however, the authors were able to discover through anecdotal report that clinicians at the

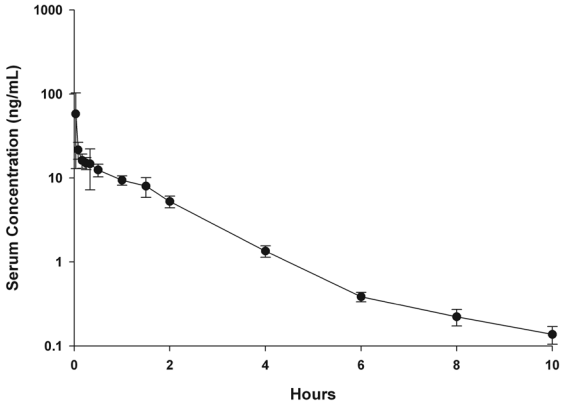

Figure 1. Serum hydromorphone concentrations (mean ± 1 SD) in 4 adult, male rhesus macaques (*Macaca mulatta*) after intravenous bolus administration of 0.075 mg/kg hydromorphone.

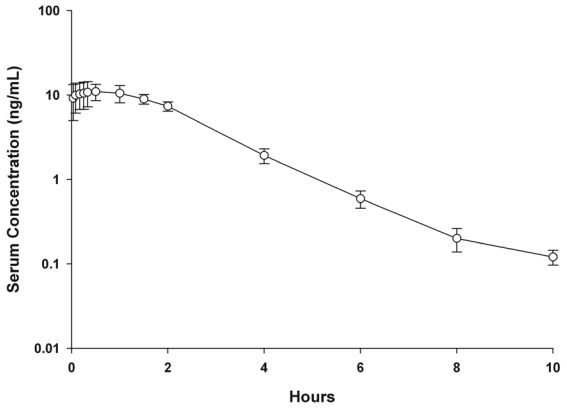

Figure 2. Serum hydromorphone concentrations (mean ± 1 SD) in 4 adult, male rhesus macaques (*Macaca mulatta*) after intramuscular bolus administration of 0.075 mg/kg hydromorphone.

Oregon National Primate Research Center use intramuscular hydromorphone for postsurgical pain management in rhesus macaques. Animals smaller than 10 kg receive 1 mg hydromorphone every 4 h for moderate to marked pain; those larger than or equal to 10 kg receive 2 mg hydromorphone every 4 h for moderate to marked pain (extrapolated hydromorphone dosing range, 0.050 to 0.400 mg/kg). Because the dose used at that facility is approximately 10-fold greater than that recommended for subcutaneous or intramuscular administration in humans[12] and because the clinical use of hydromorphone in nonhuman primates had yet to be published, on-site veterinary staff advised us to use a midrange dose for our pharmacokinetic trials. The final dose that we tested (0.075 mg/kg hydromorphone) is equivalent to a low dose for oxymorphone previously published by our laboratory to be safe in rhesus macaques.[16] We believe the parameters reported here provide additional information to the veterinary community for design of future studies to explore the incorporation of hydromorphone into evidence-based pain management protocols for nonhuman primates like the rhesus macaque.

In our intravenous trial, time points were chosen on the basis of review of previously published literature.[10,17,18] Early sampling was emphasized to capture time–concentration data that we expected to be associated with rapid narcotic drug effects (for example, respiratory depression).[9] We captured 3 distinct phases of hydromorphone, consistent with reports from normal human subjects exposed to a 45-s intravenous infusion of

Table 1. Pharmacokinetic parameters [median (range)] for hydromorphone in adult, male rhesus macaques (n = 4) after intravenous bolus administration of 0.075 mg/kg

Parameter	Estimate
A (ng/mL)	57.7 (36.6–490.9)
B (ng/mL)	16.8 (15.5–20.6)
C (ng/mL)	2.02 (1.10–2.55)
α (/min)	0.591 (0.490–0.764)
β (/min)	0.013 (0.012–0.015)
γ (/min)	0.005 (0.003–0.005)
First distribution half-life (min)	1.17 (0.908–1.41)
Second distribution half-life (min)	51.4 (47.3–58.6)
Terminal half-life (min)	142 (131–218)
Apparent volume of the central compartment (mL/kg)	1041 (147–1395)
Apparent volume of the first peripheral compartment (mL/kg)	2244 (1715–2546)
Apparent volume of the second peripheral compartment (mL/kg)	788 (556–1172)
Apparent volume of distribution at steady state (mL/kg)	4062 (2645–4907)
Clearance [(mL/min)/kg]	37.7 (33.7–47.1)
Second distribution clearance [(mL/min)/kg]	366 (70.2–479)
Third distribution clearance [(mL/min)/kg]	4.39 (3.45–4.58)
K_{10} (/min)	0.040 (0.030–0.229)
Elimination rate half-life (min)	17.7 (3.03–23.0)
K_{12} (/min)	0.386 (0.301–0.476)
K_{13} (/min)	0.004 (0.003–0.031)
K_{21} (/min)	0.158 (0.041–0.198)
K_{31} (/min)	0.006 (0.004–0.006)
Maximal serum concentration (ng/mL)	77.6 (53.8–509.4)
Area under the serum time–concentration curve (ng × min/mL)	1993 (1594–2227)
Area under the first moment curve (min*min*ng/mL)	186981 (160350–232895)
Mean residence time (/min)	97.7 (78.5–123.0)

K_{10}, K_{11}, K_{13}, K_{21}, and K_{31}: rate constants.
A, B, and C are coefficients and α, β, and γ are exponents in the equation $C_t = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$, where C_t is concentration of hydromorphone at time t.

hydromorphone.[10] Clearance in our intravenous model was similar to a previously published report in rhesus macaques (current study: median, 37.7 mL/min/kg; range, 33.7 to 47.1 mL/min/kg; previous study: median, 41.3 mL/min/kg; range 32.1 to 66.3 mL/min/kg);[17] however, additional comparisons between studies could not be made due to differences in analysis. Clearance and terminal elimination half-life of pooled multidose analysis of hydromorphone in normal, healthy human subjects have been reported to be 1.66 L/min and 184 min, respectively;[10] however, again due to differences in analytical techniques, comparisons cannot be made between our study and the cited study.[10] Regardless, we believe that our careful selection of sampling times combined with a tight inclusion cohort (that is, matched for age, sex, and body condition score) benefitted our pharmacokinetic analysis greatly, particularly with regard

Table 2. Pharmacokinetic parameters [median (range)] for hydromorphone in adult, male rhesus macaques (n = 4) after intramuscular administration of 0.075 mg/kg

Parameter	Estimate
Absorption rate constant (/min)	0.441 (0.113–0.917)
Absorption half-life (min)	1.66 (0.756–6.12)
Apparent volume of distribution (mL/kg)	5555 (3818–5998)
Rate constant (/min)	0.009 (0.007–0.009)
Elimination rate half-life (min)	81.5 (77.2–92.5)
Maximal serum concentration (ng/mL)	12.0 (11.1–18.3)
Time at which maximal serum concentration occurred (min)	9.42 (5.29–24.8)
Area under the serum time–concentration curve (ng*min/mL)	1645 (1554–2187)
Clearance/bioavailability [(mL/min)/kg]	45.6 (34.3–48.3)
Bioavailability (%)	92 (75–104)

to the interpretation of the rapid distribution and elimination phases.[9,10] The low limit of quantitation that we obtained might also have affected our analysis (for example, 0.50 ng historically in macaque and human studies[10,17] compared with 0.10 ng in the current study). We surmise that our improved assay sensitivity primarily affected the interpretation of our terminal phase results. Additional research is required to better characterize the elimination profiles of hydromorphone after intravenous administration in rhesus macaques. Additional animals may be needed ultimately to better define the absorption and elimination of hydromorphone in this species.[13]

In the intramuscular trial, absorption after intramuscular administration was rapid and similar to reports of bioavailability after subcutaneous administration of hydromorphone to rhesus macaques (92% intramuscularly compared with 97% subcutaneously).[17] No published research is available to compare intramuscular pharmacokinetic data that we present here. We noted moderate interindividual variation in bioavailability, which likely reflects the high interindividual variation frequently reported in response to opioid administration[5,10,11,25] and the small number of animals included (n = 4). Genomic variability also may have contributed to interindividual variation. We surmise that the scratching behaviors reported after both intravenous and intramuscular administration were associated with opioid-induced pruritus, as described in other studies of opioid administration in macaques.[17]

Rhesus macaques are frequently used as biomedical models for humans,[23,28] and although the analgesic effect of hydromorphone is unknown in macaques, similarities between humans and rhesus macaques are likely to exist. In humans, a log-linear dose–analgesic effect exists after intramuscular and intravenous administration of hydromorphone in doses ranging from 0.003 to 0.053 mg/kg.[5,8,10,12,20,31] Bolus administration of doses within this range has been reported to provide sufficient analgesia for both opioid-naïve, acute pain in human patients as well as opioid-exposed, chronic pain in human patients for at least 2 h.[8,10] The minimal effective plasma concentration of hydromorphone in human patients with cancer-like pain is reported to be greater than or equal to 4.0 ng/mL.[15,26] Hydromorphone concentrations between 0.400 to 6.0 ng/mL have been found to be effective in controlling acute, experimental pain in opioid-naïve, healthy humans (dosage range of 0.010 to 0.040 mg/kg in a tooth-root stimulation pain model); however, poor correlation has been reported between hydromorphone plasma concentration and effect in the clinical hospital setting with opioid-tolerant patients.[10]

To improve clinical relevance of the current study, we ran multiple simulations to estimate analgesia dosing for rhesus macaques (target goal: maintenance of hydromorphone concentrations greater than or equal to 4.0 ng/mL throughout treatment period). As such, a dose regimen of 0.200 mg/kg hydromorphone administered every 4 h is suggested for intramuscular or intravenous administration to rhesus macaques in a clinical veterinary setting. This dose is anticipated to maintain serum concentrations of greater than or equal to 4.0 ng/mL at all times except for 8 min before the second dose of intravenous administration and at all times after intramuscular administration. Lower drug concentrations may support analgesia in this species; however, species-specific analgesiometric testing ultimately is needed to develop evidence-based hydromorphone dosing recommendations. At the same time, despite the obvious need for such clinically relevant research, clinicians must always continue to recognize that patient responses to opioid analgesia are dependent on individual-specific variability of response, degree of pain, concurrent illnesses or medications, and chronicity of pain.

In summary, a 3-compartment model with bolus input in and first-order elimination from the central compartment best fit the time–concentration data after intravenous hydromorphone administration in adult male rhesus macaques. A 1-compartment model with first-order input in and first-order elimination best fit the time–concentration data after intramuscular hydromorphone administration in adult male rhesus macaques. Concentrations were maintained at greater than or equal to 4.0 ng/mL for at least 2 h in all macaques, and until analgesiometric studies are performed in this species, dosing simulations support the administration of 0.200 mg/kg hydromorphone every 4 h either intramuscularly or intravenously for rhesus macaques.

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