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Pharmacokinetic Profiles of Gabapentin after Oral and Subcutaneous Administration in Black-tailed Prairie Dogs (*Cynomys ludovicianus*)

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In veterinary and human medicine, gabapentin (a chemical analog of γ-aminobutyric acid) is commonly prescribed to treat postoperative and chronic neuropathic pain. This study explored the pharmacokinetics of oral and subcutaneous administration of gabapentin at high (80 mg/kg) and low (30 mg/kg) doses as a potential analgesic in black-tailed prairie dogs (*Cynomys ludovicianus*; *n* = 24). The doses (30 and 80 mg/kg) and half maximal effective concentration (1.4 to 16.7 ng/mL) for this study were extrapolated from pharmacokinetic efficacy studies in rats, rabbits, and cats. Gabapentin in plasma was measured by using an immunoassay, and data were evaluated using noncompartmental analysis. The peak plasma concentrations (mean ± 1 SD) were 42.6 ± 14.8 and 115.5 ± 15.2 ng/mL, respectively, after 30 and 80 mg/kg SC and 14.5 ± 3.5 and 20.7 ± 6.1 ng/mL after the low and high oral dosages, respectively. All peak plasma concentrations of gabapentin occurred within 5 h of administration. Disappearance half-lives for the low and high oral doses were 7.4 ± 6.0 h and 5.0 ± 0.8 h, respectively. The results of this study demonstrate that oral administration of gabapentin at low (30 mg/kg) doses likely would achieve and maintain plasma concentrations at half maximum effective concentration for 12 h, making it a viable option for an every 12-h treatment.

Abbreviations: CL, clearance; F, absolute bioavailability; V_d, volume of distribution

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The black-tailed prairie dog (*Cynomys ludovicianus*) is a North American rodent used at the Centers for Disease Control and Prevention for monkeypox virus studies due to their ability to mimic the manifestation of human monkey pox.[11] Monkeypox virus is currently the most important *Orthopoxvirus* genus in terms of human health.[5] Since the 2003 outbreak of human monkeypox virus in the United States, prairie dogs' use as a biomedical infectious disease model has made significant contributions to the medical community's understanding of the pathogenesis of human orthopoxvirus infections and has aided in the development of novel vaccines.[5,12,17,28,29] Other areas of biomedical research using black-tailed prairie dogs include hepatobiliary disease, clostridial diarrhea, oxygen consumption, and hibernation research.[32] In addition, black-tailed prairie dogs can be found in many North American homes as nondomesticated companion animals.

Despite the use of prairie dogs in research over the past 2 decades, analgesics are used infrequently in this species, in part because of the lack of data regarding appropriate doses. Gabapentin is one of the commonly prescribed analgesics for neuropathic and chronic pain (that is, osteoarthritic, cancer) in small animals.[1] In biomedical research, gabapentin is extensively used in surgical peripheral and central nerve injury models due to the drug's neuroprotective properties (i.e., Schwann cell proliferation, axonal degeneration) and antiinflammatory activity via the release of antioxidants (i.e., superoxide dismutase, glutathione, nitric oxide) during reperfusion injury.[22,26,27] This analgesic effect is the result of the drug's binding to the α2δ ligands of calcium-voltage–gated subunit receptors and reducing excitatory neurotransmitter secretions (i.e., substance P, norepinephrine, epinephrine).[2,8,23,30]

In light of previous pharmacokinetic studies investigating analgesics (i.e., single-dose meloxicam, sustained-released meloxicam, sustained-release buprenorphine) in black-tailed prairie dogs, extrapolating standard doses from other species has limited utility due to an atypical response observed in prairie dogs.[4,12,23,31] Meloxicam is a semi-selective cyclooxygenase 2 inhibitor NSAID routinely used at 0.2 to 4 mg/kg SC in many rodent species.[4,9,18,25,32] In black-tailed prairie dogs, meloxicam at recommended doses resulted in subtherapeutic concentrations,[4] and higher doses resulted in excessively high plasma concentrations with insufficient elimination.[12,23] Adverse effects of NSAID include gastrointestinal effects (i.e., anorexia, diarrhea, melena) and renal toxicity (i.e., renal failure).[25] Sustained-release buprenorphine, a partial μ agonist opioid, achieved therapeutic levels beyond 72 h in black-tailed prairie dogs at doses comparable to those in rodent species (0.5 mg/kg SC);[4,12,18] however, dermal reactions at the injection site were noted in both dose groups.[4,12] Furthermore, adverse effects such as hyperalgesia, weight loss, anorexia or pica, and respiratory depression occurred after buprenorphine administration in rodents.[21] In addition, the human opioid endemic has placed a burden on pharmaceutical companies and subsequently veterinary medicine. Sustained-release

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buprenorphine, a Schedule III narcotic, currently is available only to DEA-registered veterinarians through a single compounding company, thus posing a significant challenge with diversion of these drugs to field or laboratory investigators. Alternatively, gabapentin has a wider margin of safety and is not classified as a federally controlled substance, such that veterinarians can legally prescribe or dispense this analgesic to field or laboratory researchers and pet owners without the burden of federal regulatory oversight, potential human dependence from abuse, or shortage of availability.[24]

Therefore, determining the pharmacokinetic profile of gabapentin in black-tailed prairie dogs is necessary for appropriately managing pain and safety in this rodent species. Current literature suggests that the drug's average half-life is 2 to 7 h after oral administration in other animals (i.e., dogs, cats, humans, horses), but the associated dosing frequency is less than ideal in laboratory settings,[1,24] particularly during in vivo monkeypox studies, which require BSL3 containment. Although black-tailed prairie dogs are used in research, they are nonetheless a nondomesticated animal, and frequent handling increases the amount of stress placed on these animals.[3,4,6,7,10-13,32] The aim of the current study was to investigate the pharmacokinetics of oral and subcutaneous administration of gabapentin at high (80 mg/kg) and low (30 mg/kg) doses. We hypothesized that the subcutaneous formulations would sustain half-maximal concentrations longer than oral formulations and without side effects (i.e., ataxia, dermal reactions, muscle tremors), as determined through previous pharmacoefficacy studies in other species.[1,11,19,20,27]

Materials and Methods

Animals. The study protocol was approved by the Centers for Disease Control and Prevention IACUC. The work was performed in a USDA-registered, OLAW-assured, and AAALAC-accredited animal facility in accordance with the *Guide for the Care and Use of Laboratory Animals*.[14] Wild-caught male and female black-tailed prairie dogs (*Cynomys ludovicianus*; $n = 24$; age, approximately 2 y; weight, 800 to 1200 g) were obtained from a vendor in Texas that used humane live-trapping techniques. All animals were quarantined for 30 d, microchipped for identification, and physically examined prior to being placed in floor-housed pens and maintained in climate-controlled rooms on a 12:12-h light cycle with a room temperature of 20 to 23 °C and humidity of 30% to 70%, to simulate a natural environment. Animals had ad libitum access to a commercial prairie dog diet (Brisky, Franklinville, NY, or Exotic Nutrition, Newport News, VA) and distilled water via bottles.

Prior to single housing, the animals were weighed and sexed, and a blood sample (prebleed, time point 0) was collected from the lateral saphenous vein of each animal. For animals ($n = 12$) randomly selected for the subcutaneous group, the hair between the scapula blades was removed with clippers and cleaned with ethanol to allow for aseptic injections and observations of any dermal reactions to the compound after injection. Animals were single-housed in IVC (18.62 m^2, GR1800 Double Decker Unit, Tecniplast, West Chester, PA). Each cage contained crinkle paper, a cardboard tunnel, and as an extra source of fluids, diet-gel (ClearH_2O, Portland, ME) mixed with peanut butter to increase palatability. A 72-h acclimation period was allotted for each animal prior to the start of the serial bleeds (at 1, 2, 4, 8, 12, and 24 h after drug administration).

Drug administration and phlebotomy. By using stratified random sampling, 24 prairie dogs were selected into 4 dosage groups, (each contained 3 females and 3 males): oral low dose (30 mg/kg PO); oral high-dose (80 mg/kg PO); subcutaneous low dose (30 mg/kg SC); and subcutaneous high dose (80 mg/kg SC). The gabapentin dosages selected were based on previous studies in rodents, lagomorphs, and felines.[1,11,19,20,27] The criteria for dose selection were safety and efficacy in providing reversal of mechanical hyperalgesia and thermal allodynia in rodent species.[8] Route of administration was based on practicality of administration in conscious and anesthetized animals. Gabapentin (400-mg capsules; Neurontin, Ascend Laboratory, Parsippany, NJ) and gabapentin USP (0.8 mg; Medisca, Plattsburgh, NY lot nos. 102418 to 105736) were compounded by a pharmacist into suspensions for this study. For the oral suspension, gabapentin (80 mg/mL) was formulated by adding 15 capsules to 30 mL of Ora Plus (Medisca, Plattsburg, NY), 6 to 10 mL of Ora-Sweet (Medisca), 1 mL of peanut butter flavor (FlavoRx, Columbia, MA), 0.1 g of natural bitterness masking powder (Fargon, St Paul, MN), and 2 mL of sweetening enhancer (FlavoRx, Columbia, MA). For subcutaneous suspension, 0.08 grams of gabapentin USP and 0.16 grams of sodium chloride were dissolved in 20 mL of sterile water for injection. The mixture was then filtered through a 0.22-µm filter (lot no. 13314180, Supor membrane, Pall Laboratory, Port Washington, NY) into a sterile, single-use serum vial to achieve a concentration 40 mg/mL. Each compounded product was inverted several times to produce a homogenous dose prior to administration. No assays were performed to verify the accuracy of the final compounded products.

Animals were anesthetized with 1% to 5% isoflurane in their respective IVC before being transferred to the working table, maintained on a tightly fitting facemask, and continuously monitored until awake. The selection of isoflurane inhalant as the general anesthetic agent was due to its high safety margin, as demonstrated in several studies.[4,7,8] Animals in the oral dosing group received their medication via oral gavage with a reusable oral gavage needle (either 10 gauge × 50.8 mm or 16 gauge × 38.1 mm; Perfektum, New Hyde Park, NY); animals in the subcutaneous dosing group received their injections through a 25-gauge needle between the shoulder blades. Blood (0.2 to 0.5 mL per time point) was collected into K_2EDTA Microtainer collection tubes (lot no. 8031772, Becton Dickenson, Franklin Lakes, NJ) by using a 25- or 26-gauge needle. Blood was collected from the medial saphenous or cranial vena cava at 1, 2, 4, 8, 12, and 24 h after drug administration. Blood samples were centrifuged at 300 × *g* for 10 min; approximately 200 mL of plasma was transferred into cryotubes and stored at –80 °C until analyzed. After drug administration, animals were monitored up to 72 h for adverse effects, including vomiting, diarrhea, lethargy, and ataxia.

Pharmacokinetic analysis and statistics. Gabapentin was detected and quantified in prairie dog serum by using an FDA-approved human immunoassay on a general chemistry analyzer. The assay was validated through Auburn University's Clinical Pharmacology Laboratory by using pooled black-tailed prairie dog serum to which known concentrations of gabapentin (0 to 41.6 ng/mL) were added. The upper and lower limits of the curve were based on those used in humans and were confirmed based on the coefficient of variation of the predicted compared with known concentrations of the controls. The upper and lower limits of quantitation are 40 and 1 ng/mL, respectively. The coefficient of variation was less than 35% for the low end of the control range and less than 8% for the high end.

Plasma gabapentin concentration compared with time data underwent noncompartmental analysis by using computer software (version 8.1, Phoenix WinNonLin, Pharsight, Mountain

View, CA). The $AUC_{0\text{-inf}}$ was determined by using the log-linear trapezoidal method. The actual C_{max} and T_{max} were recorded. The slope of the terminal component of the drug-elimination time curve was based on nonlinear regression. Because gabapentin was not given intravenously, the terminal component could not be confirmed to be eliminated. Consequently, both the elimination rate constant and half-life were reported in terms of disappearance; half-life was reported as harmonic mean ± pseudoSD. Furthermore, neither clearance (CL) nor the volume of distribution (V_d) could be determined and are reported as a ratio relative to absolute bioavailability (F). Other parameters included mean residence time and the percentage of the AUC that was extrapolated from the terminal component of the curve. The relative bioavailability of the oral compared with subcutaneous dose was calculated according to the ratio of the mean $AUC_{oral}/AUC_{subcutaneous}$ at each dose.

Prism (version 8.0.0 for Windows, GraphPad Software, San Diego, CA) was used for statistical analysis and summarization. Intragroup (i.e., sex, time) and intergroup (i.e., dosage) comparisons were conducted on the pharmacokinetic profiles of both administration modes of gabapentin. Using ANOVA with multiple comparison, we identified any *P* value of less than 0.05 as significant. EC_{50} values were determined from pharmacodynamics and pharmacy efficacy studies conducted in rodents and other small mammals.[1,8,19,20,27] Although published EC_{50} values for prairie dogs are unavailable currently, gabapentin plasma concentrations that fell between the extrapolated EC_{50} (1.4 to 16.7 ng/dL) were assumed to be sufficient for an analgesic response.

Results

All prairie dogs in this study tolerated both doses and administration routes of gabapentin. No injection site or adverse reactions were noted. Results of the pharmacokinetics analysis are summarized in Table 1. Mean plasma time compared with the concentration profiles of oral and subcutaneous gabapentin are summarized in Figure 1. For all groups, plasma levels peaked within the first 5 h; T_{max} did not differ significantly with regard to route or dose. The mean C_{max} of gabapentin differed significantly ($P < 0.05$) between routes of administration (Table 1). The peak C_{max} of gabapentin after subcutaneous administration demonstrated a significant dose-dependent relationship ($P < 0.0001$). C_{max} did not differ between the 2 oral doses of gabapentin administration ($P = 0.9$). We were unable to detect plasma levels in one or more animals per group at 24 h; however, a sufficient number of samples were measured accurately to define the terminal component of the AUC. The 95% CI for the effect of sex was –0.5 to 0.5, thus indicating that half-life does not differ according to the animal's sex and that route and dose effects are similar between males and females. The mean half-life for gabapentin is 0.7 to 1.6 h shorter (with 95% confidence) when the drug was administered subcutaneously than when given orally. The half-life was 0.3 to 1.0 h longer (with 95% confidence) on average with the 80-mg/kg dose than the 30-mg/kg dose. Mean clearance (CL/F) of gabapentin was significantly ($P < 0.05$) greater after oral than subcutaneous administration. The relative bioavailability after oral compared with subcutaneous administration was 40% at 80 mg/kg and 61% at 30 mg/kg. Our AUC percentage extrapolated was less than 12% for all dosages (Figure 1).

Discussion

This study assessed 2 doses and routes of gabapentin administration in black-tailed prairie dogs. We extrapolated the doses and routes used in our study from previous pharmacokinetic profiles of gabapentin in rodents, lagomorphs, and felids.[1,15,16,19] To our knowledge, no previous studies described the half maximal effective concentration for gabapentin in prairie dogs, but that for rodents is 1.4 to 16.7 ng/mL.[1,8,16] We were unable to locate any literature regarding the pharmacokinetics of gabapentin in rodents of the Sciuridae family, of which the black-tailed prairie dog is a member, or similar wildlife rodent species for comparison.

Our findings indicated that oral administration of gabapentin at 30 mg/kg sustained half maximal effective concentrations longer than did subcutaneous administration of the same dose. Additional findings from our study on oral administration of gabapentin to prairie dogs indicate dose-dependent saturation and poor bioavailability, thus supporting previous studies conducted in humans and small animals.[1,2] In our study, oral administration of 30 mg/kg gabapentin achieved mean plasma concentrations exceeding 1.4 ng/mL for at least 12 h in black-tailed prairie dogs; all other dosages achieved mean peak plasma concentrations that exceeded our half maximal effective concentration. Moreover, no adverse clinical signs (i.e., ataxia, dermal reactions, peripheral edema, muscle tremors) were observed in animals that received any dosage; however, clinical assessment tools (i.e., blood chemistries and CBC) were not performed to determine the effects of these formulations on organ function.

A limitation of this study was the exclusion of gabapentin administered intravenously. Consequently, we were unable to report intravenous reference parameters such as elimination, clearance, and apparent volume of distribution. We did not test intravenous administration due to the impracticality of this administration method and lack of vascular access when considering the frequency of serial bleeds. Without these additional parameters, we cannot exclude a 'flip-flop' pharmacokinetic effect due to extravascular drug administration of gabapentin. A "flip flop" effect occurs when the rate of absorption is slower than the rate of elimination; in this case, the terminal component actually reflects absorption and the proximal portion, elimination. Flip-flop pharmacokinetic modeling is useful when the rate of absorption closely parallels the plasma–time concentration. Given the poor bioavailability of orally administered gabapentin and lack of intravenous references to determine elimination rate, the elimination rate constant that we report likely exceeds the absorption rate. However, we cannot determine the steady-state plasma concentrations of gabapentin after a single administration; a study using both repeated dosing and a single intravenous dose would be needed to recommend adequate plasma concentrations for an undetermined duration.

In addition, the inability to accurately report elimination and clearance data complicates the interpretation of undetectable gabapentin plasma concentrations in several animals. Two prairie dogs (one of each sex) that received gabapentin orally at high and low doses had undetectable plasma concentrations at 24 h. In addition, 3 animals (2 males at the high dose and one female at the low dose) that received gabapentin subcutaneously had undetectable concentrations at 24 h. Therefore, we cannot attribute the undetectable plasma levels solely to clearance or elimination because heteroscedasticity must also be considered.

The results of this study provide useful insight for future studies of the pharmacokinetics of gabapentin in black-tailed prairie dogs. Although not statistically significantly different, oral administration of gabapentin demonstrated a longer half-life than subcutaneous administration; this is relevant to our goal of achieving a half maximum effective concentration

Table 1. Mean values from pharmacokinetics analysis

Route and dose	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}inf}$ (h × ng/mL)	$AUC_{0\text{-}extrap}$ (%)	$MRT_{0\text{-}inf}$ (h)	$HL_{\lambda z}$ (h)	λ_z (1/h)	CL/F (mL/h/kg)	Vz/F (mL/kg)
Oral, 30 mg/kg	14.45[a]	3.88	152.92	11.81	12.32	7.39	0.13	312.1[a]	3707.9
Oral, 80 mg/kg	20.65[a]	5.17	252.88	7.82	9.85	4.98	0.14	441.2[a]	3084.2
Subcutaneous, 30 mg/kg	42.5[a]	1.02	247.15	2.26	5.43	3.18	0.22	152.2[a]	684.1
Subcutaneous, 80 mg/kg	115.45[a]	1.36	620.18	2.15	5.32	3.58	0.20	144.6[a]	737.2

λz, disappearance rate constant; AUC0-extrap, percentage of AUC extrapolated that was observed; AUC0-inf, AUC from time observed to infinity; Cmax, maximal concentration; Cl/F, nonadjusted clearance; HLλz, disappearance half-life; MRT0-inf, mean residence time; Tmax, time at Cmax; Vz/F, nonadjusted volume of distribution of the central compartment.
a, $P < 0.05$, route of administration comparison

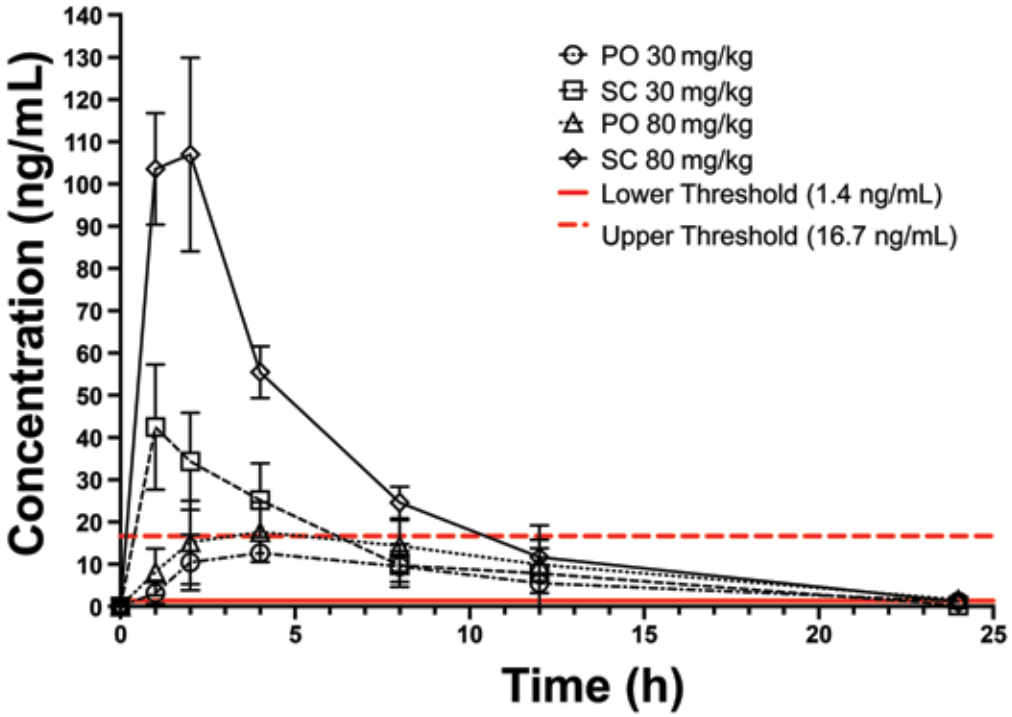

Figure 1. Mean plasma concentrations of gabapentin over time after its administration at 30 mg/kg PO, 80 mg/kg PO, 30 mg/kg SC, and 80 mg/kg SC in 24 black-tailed prairie dogs. Samples were collected at 1, 2, 4, 8, 12, and 24 h after administration of gabapentin. Bars, 1 SD.

(1.4–16.7 ng/mL), which has been proven to provide analgesia in other rodents.[1,8,19,20,27] Only the low dose of oral gabapentin maintained this concentration without exceeding it.

The poorer bioavailability after oral compared with subcutaneous administration is likely responsible for the pharmacokinetic modeling; however, information on intravenous elimination is necessary to test this possibility. Furthermore, the pharmacokinetic parameters of the subcutaneous administration groups were linear, suggesting a more predictable response and lower probability of possible adverse effects than for oral administration. The aforementioned limitations should be considered by clinicians and researchers prior to using gabapentin in prairie dogs. As shown with previous studies,[23] coadministration of gabapentin as part of a multimodal analgesic plan results in lower half maximal effective concentrations, as seen with more commonly prescribed analgesics (i.e., opioid substances).[23] In addition, the durations of effects and half-life of gabapentin in multimodal regimens should be investigated in future studies, given the pharmacokinetics of other analgesics (i.e., sustained-release buprenorphine) in black-tailed prairie dogs. After necessary efficacy and safety refinements, future perioperative analgesic regimens involving gabapentin include the use of oral or subcutaneous administration as viable options. In conclusion, pharmacoefficacy and pharmacodynamics studies of gabapentin administration in prairie dogs as a monotherpeutic and when combined in multimodal analgesic regimens are necessary for validation of the half maximal effective concentration data that we obtained here.

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